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TITLE PAGE

REVIEW ARTICLE

Epigenetic Regulation of MDR1 and BCRP Transporters by HDAC Inhibition

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Abbreviations (alphabetical order):

5-azacytidine, 5aC; Amyloid-β, Aβ; ATP-binding cassette, ABC; aryl hydrocarbon receptor, AHR; acute lymphoblastic leukemia, ALL; acute myeloid leukemia, AML; blood-brain barrier, BBB; breast cancer resistance protein, BCRP; β-naphthoflavone, βNF; constitutive androstane receptor, CAR; chronic myelogenous leukemia, CML; dioxin response element, DRE; downstream promoter, DSP; histone acetyltransferase, HAT; human brain microvascular endothelial, hCMEC/D3; histone deacetylase, HDAC; human embryonic kidney 293, HEK; multidrug resistance protein 1, MDR1; multidrug resistance-associated protein, MRP; membrane spanning domain, MSD; nicotinamide adenine dinucleotide, NAD; nucleotide binding domain, NBD; nuclear transcription factor Y, NF-Y; NF-Y alpha subunit, NF-YA; P300/CBP-associated factor, PCAF; phosphatidylinositol 3-kinase, PI3K; pregnane X receptor, PXR; suberoylanilide hydroxamic acid, SAHA; short chain fatty acid, SCFA; sirtuin, SIRT; transmembrane domain, TMD; trichostatin A, TSA; transcription start site, TSS; untranslated region, UTR; valproic acid, VPA

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ABSTRACT

Multidrug resistance protein 1 (MDR1, *ABCB1*, P-glycoprotein) and breast cancer resistance protein (BCRP, *ABCG2*) are key efflux transporters that mediate the extrusion of drugs and toxicants in cancer cells and healthy tissues including the liver, kidneys, and the brain. Altering the expression and activity of MDR1 and BCRP influences the disposition, pharmacodynamics, and toxicity of chemicals including a number of commonly prescribed medications. Histone acetylation is an epigenetic modification that can regulate gene expression by changing the accessibility of the genome to transcriptional regulators and transcriptional machinery. Recently, studies have suggested that pharmacological inhibition of histone deacetylases (HDACs) modulates the expression and function of MDR1 and BCRP transporters as a result of enhanced histone acetylation. This review addresses the ability of HDAC inhibitors to modulate the expression and the function of MDR1 and BCRP transporters, and explores the molecular mechanisms by which HDAC inhibition regulates these transporters. While the majority of studies have focused on histone regulation of MDR1 and BCRP in drug-resistant and drug-sensitive cancer cells, emerging data point to similar responses in non-malignant cells and tissues. Elucidating epigenetic mechanisms regulating MDR1 and BCRP is important to expand our understanding of the basic biology of these two key transporters and subsequent consequences on chemoresistance as well as tissue exposure and responses to drugs and toxicants.

Significance Statement

Histone deacetylase inhibitors alter the expression of key efflux transporters MDR1 and BCRP in healthy and malignant cells.

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1. INTRODUCTION

Transporters facilitate the transcellular movement of various substrates and are classified based on the molecular mechanisms, energetics, and directionality of transfer across the plasma membrane. ATP-binding cassette (ABC) transporters are a superfamily of primary active transporters that utilize energy generated by the hydrolysis of ATP. Upon substrate binding to the transporter, ATP binds to the nucleotide binding domain (NBD) of the transporters to change the protein's conformation to facilitate the transfer of substrates to the extracellular space (Sharom, 2008). In mammals, ABC transporters mediate the efflux of various endo- and xenobiotics. Key ABC transporters, including the multidrug resistance protein 1 (MDR1, *ABCB1*, P-glycoprotein, Pgp), breast cancer resistance protein (BCRP, *ABCG2*), and multidrug resistance-associated proteins (MRPs, *ABCCs*), play critical roles in regulating the passage of chemicals in kidney proximal tubules, enterocytes, hepatocytes, and brain endothelial capillary cells (Klaassen and Aleksunes, 2010). Modulating the expression and activity of these transporters can influence the tissue kinetics, pharmacology, and toxicity of substrates. Transcriptional regulation of efflux transporters has been widely known and comprehensively covered in several reviews (Kullak-Ublick and Becker, 2003; Miller, 2010; Pavek and Smutny, 2014; Amacher, 2016). Recently, there has been growing evidence for epigenetic mechanisms, particularly histone acetylation, that can regulate the MDR1 and BCRP transporters. This review highlights key findings regarding the epigenetic regulation of MDR1 and BCRP expression and function by modulating histone acetylation.

2. MULTIDRUG RESISTANCE PROTEIN 1 (MDR1)

2.1. Biochemical and Physiologic Characteristics of MDR1

MDR1 is a 170 kDa N-glycosylated protein composed of 1,280 amino acids. It is comprised of two homologous parts, each of which is comprised of a six-segment transmembrane domain (TMD) and a cytoplasmic NBD where ATP binding and hydrolysis occur (van der Bliek et al., 1988; Devault and Gros, 1990; Aller et al., 2009). A flexible linker connects the C-terminal of the TMD of one half with the N-

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terminal of the NBD of the other half. MDR1 is encoded by one gene in humans (*MDR1/ABCB1*) while there are two genes, *Mdr1a/Abcb1a* and *Mdr1b/Abcb1b,* that encode mouse Mdr1 (Gros et al., 1986a; Gros et al., 1986b; Ueda et al., 1986; Hsu et al., 1989). There is a high level of sequence similarity (approximately 75%) between the human MDR1 and mouse Mdr1 proteins (Chen et al., 1986; Gerlach et al., 1986; Gros et al., 1986a; Ueda et al., 1987b).

MDR1 is expressed at high levels in epithelial cells of the colon, small intestine, kidney proximal tubules and bile ductules, and endothelial cells of the blood-testis barrier, blood-brain barrier (BBB), blood-mammary tissue barrier, and blood-inner ear barrier (Fojo et al., 1987; Thiebaut et al., 1987). Its expression has been also detected on the luminal surface of the pregnant endometrium as well as placental trophoblasts (Lankas et al., 1998; St-Pierre et al., 2000). The distribution of mouse Mdr1a and Mdr1b combined together approximate the expression profile of human MDR1 (Cornwell, 1991; Klaassen and Aleksunes, 2010). A wide range of compounds is handled by the MDR1 transporter. Generally, MDR1 substrates are large (250 Da to 1850 Da) and hydrophobic or weakly amphipathic compounds (Schinkel, 1999). Structurally, many substrates contain planar aromatic rings but there are also nonaromatic compounds transported by MDR1. Inhibitors of MDR1 can be similarly structured as substrates leading to competitive inhibition of the transporter, while others exert noncompetitive inhibition properties (Schinkel, 1999; Seelig and Landwojtowicz, 2000; Wang et al., 2003; Sharom, 2006; Sharom, 2008). The mouse Mdr1 isoform has a largely similar substrate specificity as the human MDR1 transporter (Ambudkar et al., 1999; Schinkel, 1999). Examples of MDR1 substrates and inhibitors are listed in **Table 1**.

2.2. Clinical Importance of MDR1

MDR1 is not essential for basic physiological function as Mdr1 knockout mice are fertile and phenotypically healthy (Schinkel et al., 1997). However, MDR1 imparts important function in determining exposure and consequently, cellular responses to MDR1-transported drugs or toxicants. For example, in MDCKII tubule cells transfected with the *ABCB1* gene, the basolateral-to-apical transport (efflux) of the tyrosine kinase inhibitor gefitinib was significantly increased compared to matched control cells (Agarwal

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et al., 2010). In the presence of the MDR1 inhibitor, LY335979, the efflux of gefitinib in MDR1-transfected cells was reduced to the same level as observed in control cells. Also, the oral bioavailability of the chemotherapeutic drug paclitaxel was significantly higher in Mdr1a knockout mice, potentially due to reduced epithelial efflux of paclitaxel into the intestinal lumen (Sparreboom et al., 1997). The roles of MDR1 influencing the transport and the toxicity of kidney toxicants have been well-demonstrated, as reviewed by George and colleagues (George et al., 2017). The modulation of chemical transport by MDR1 is also important for the brain which is a tightly controlled environment with generally low penetration of chemicals. For instance, Mdr1a/1b knockout mice exhibit higher total brain, as well as brain-to-plasma, concentrations of the MDR1 substrate and analgesic morphine (Xie et al., 1999). In humans, a loss-of-function *ABCB1* rs9282564 genetic polymorphism is associated with more significant adverse drug events from morphine including respiratory depression (Sadhasivam et al., 2015). MDR1 has been also implicated as an efflux transporter for amyloid-β (Aβ), a key constituent of pathological plaques in patients with Alzheimer's Disease. Wang et al. showed that Mdr1a knockout mice accumulate greater Aβ concentrations in their brains compared to wild-type mice (Wang et al., 2016). Collectively, it is critical to understand the regulation of MDR1 function as it is a determining factor influencing tissue levels of drugs and toxicants.

2.3. Transcriptional Regulation of MDR1

MDR1 expression and function can be regulated at the transcriptional and post-transcriptional levels. The transcription of MDR1, which is encoded by *ABCB1,* is mediated by the coordinated action of different transcription factors at the *ABCB1* promoter. The *ABCB1* gene is located on chromosome 7q21.1, has two distinct promoters, an upstream promoter, which is located at the beginning of the exon -1, and a downstream promoter (DSP), which resides within exon 1 (Roninson et al., 1986; Ueda et al., 1987a; Ueda et al., 1987b; Cornwell, 1990; Cornwell, 1991). The DSP generates the major transcript and is preferentially transcribed (**Figure 1**). There are several response elements at the DSP for transcription factors to bind and stimulate gene activation. The DSP is characterized by the lack of a TATA-box, which is typical for human

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drug transporter genes (Ueda et al., 1987b; Cornwell, 1991; Scotto, 2003). Instead, the initiator sequence (-6 to +11 bp relative to transcription start site (TSS)) surrounding the TSS plays a role in directing gene activation (van Groenigen et al., 1993). The initiator interacts with RNA polymerase II and facilitates the recruitment of a transcription factor IID complex to efficiently begin gene transcription (Pugh and Tjian, 1991; van Groenigen et al., 1993). Analysis of promoter activity using the deletion mutations suggests that the sequence from -134 to +286 bp relative to the TSS is important for an efficient and high rate of transcription for the *ABCB1* gene (Cornwell, 1990; Goldsmith et al., 1993; Madden et al., 1993).

Indeed, there are several response elements located within the *ABCB1* region -134 to +286 bp to mediate the binding of key transcription factors. There exists a CCAAT box-like sequence (-118 to -113 bp) as well as an inverted CCAAT box or Y box (-82 to -73 bp) which is crucial for the basal expression of the *ABCB1* gene (Ueda et al., 1987b; Ogura et al., 1991; Goldsmith et al., 1993; Sundseth et al., 1997; Jin and Scotto, 1998; Gromnicova et al., 2012). Y box is a binding site for nuclear transcription factor Y (NF-Y). NF-Y was shown to interact with P300/CBP-associated factor (PCAF), a transcriptional co-activator with intrinsic histone acetyltransferase (HAT) activity, to induce the histone acetylation at the promoter and facilitate gene transcription (Jin and Scotto, 1998). There are also GC boxes (-110 to -103 bp, -61 to -51 bp) which interact with Sp1 and Sp3 transcription factors (Ueda et al., 1987b; Cornwell and Smith, 1993; Sundseth et al., 1997; Gromnicova et al., 2012). An AP1 response site (-121 to -115 bp) was also identified and found to be involved in the transcriptional activation of *ABCB1* (Daschner et al., 1999). The presence of response elements for xenobiotic-activated transcription factors has also been described. There are two putative dioxin response elements starting at -55 bp and at +238 bp (with a single base mismatch), which are binding sites for aryl hydrocarbon receptor (AHR)/AHR nuclear translocator heterodimers (Ueda et al., 1987b; Denison et al., 1988; Madden et al., 1993; Chan et al., 2013b). AHR is a ligand-activated transcription factor that has been consistently shown to mediate *ABCB1* transcription in several tissues. Ligands of AHR include carcinogens such as 2,3,7,8-tetrachlorodibenzodioxin and benzo(*a*)pyrene as well as flavonoid compounds including β-naphthoflavone (βNF) (Murray et al., 2014). A pregnane X receptor (PXR) response element was also found to be located distally in the -8kb upstream enhancer (Geick et al.,

2001). Within the *ABCB1* promoter, there are also binding motifs for stress-induced regulators of MDR1 expression including NF-κB (-167 to 158 bp) and p53 (-72 to -40 bp) (Chin et al., 1992; Thottassery et al., 1997; Deng et al., 2001; Johnson et al., 2001; Sampath et al., 2001). Cooperative interactions between the initiator and different response elements upstream of the TSS are necessary for precise and accurate transcriptional initiation (Scotto, 2003).

Unlike the human *ABCB1* gene, mouse *Abcb1* genes, located on chromosome 5, do contain a TATA-box upstream of the TSS, but overall, there is a high sequence similarity between human *ABCB1* and mouse *Abcb1* (Raymond and Gros, 1989; Hsu et al., 1990; Cornwell, 1991). Two mouse *Mdr1* genes, *Abcb1a* and *Abcb1b*, are also highly similar in sequence to each other, sharing common *cis*-acting regulatory elements. Both *Abcb1a* and *Abcb1b* have CCAAT boxes as well binding sites for AP1 and Sp1 upstream of the TSS, although the exact locations and abundance differ between two genes (Hsu et al., 1989; Raymond and Gros, 1989; Hsu et al., 1990; Raymond and Gros, 1990; Cohen et al., 1991). However, Hsu and coworkers illustrated an important difference between the two isoforms. They found that the transcription of *Abcb1a*, like that of human *ABCB1*, can be mediated by the two distinct promoters, upstream and downstream (Hsu et al., 1990). The downstream promoter produces the major transcripts which are detected at high levels in normal tissues expressing *Abcb1a*. Consequently, variants of transcripts were generated by the *Abcb1a* gene in certain cells, while a single transcript was associated with *Abcb1b* (Cohen et al., 1991).

Xenobiotic-activated receptors, such as Pxr and Ahr, are also noted as potential regulators of mouse Mdr1. The protein expression of mouse Mdr1 was significantly up-regulated in brain microvessels of adult mice treated with dexamethasone, which is a Pxr and glucocorticoid receptor ligand (Chan et al., 2013a). Also, a recent study showed that pregnenolone 16α-carbonitrile, a ligand of murine Pxr, was able to differentially regulate both mRNA and protein expression of Mdr1 in intestine, liver, and cortex tissues of mice (Yamasaki et al., 2018). An Ahr activator, 3-methylcholanthrene, was also shown to induce the mRNA level of *Abcb1b* in Hepa-1c1c7 mouse hepatoma cells. Furthermore, potential dioxin response elements (DREs) interacting with Ahr were identified at the distal location of *Abcb1b* promoter (Mathieu et al., 2001).

Lastly, studies also showed the capability of p53 to differentially regulate rodent *Abcb1a* and *Abcb1b* expression (Thottassery et al., 1997; Lecureur et al., 2001).

In summary, *MDR1* gene regulation involves the interaction of multiple transcription factors at the *ABCB1* promoter which affect gene transcription. Although, the structural features of promoters for human *ABCB1* and mouse *Abcb1* genes have some differences, the pathways involved in the transcriptional regulation of *ABCB1* and *Abcb1* genes appear to be similar.

3. BREAST CANCER RESISTANCE PROTEIN (BCRP)

3.1. Biochemical and Physiologic Characteristics of BCRP

BCRP is a 72kDa half-transporter that is 655 amino acids in length. It has one N-terminal NBD and one C-terminal six-segment TMD (Allikmets et al., 1998; Taylor et al., 2017; Jackson et al., 2018). The half-transporter forms a homodimer through disulfide bond formation, an event required for efflux function (Henriksen et al., 2005; Wakabayashi et al., 2006; Khunweeraphong et al., 2017). BCRP is encoded by the *ABCG2* gene in humans and the *Abcg2* gene in rodents (Bailey-Dell et al., 2001; Tanaka et al., 2005; Natarajan et al., 2011).

BCRP is widely expressed across different tissues and generally serves a protective function similar to the MDR1 transporter. The highest expression of BCRP is detected at the apical surface of the syncytiotrophoblasts in the placenta where the transporter plays a major role in protecting the fetus from exposure to toxic substrates transferred from the maternal blood (Maliepaard et al., 2001; Mao, 2008; Pollex et al., 2008). BCRP is also localized at the apical surfaces of hepatocytes, kidney proximal tubule cells, and enterocytes (Maliepaard et al., 2001; Jonker et al., 2002). Additionally, it is expressed at the blood-testis barrier and the BBB (Cooray et al., 2002; Bart et al., 2004; Enokizono et al., 2008). Mouse Bcrp is expressed in similar types of tissues as humans, though to varying levels. For example, mouse Bcrp is more highly expressed in the kidneys than in the placenta (Tanaka et al., 2005).

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The substrate specificity of BCRP transporter has a comparable overlap with that of the MDR1 transporter. Like MDR1, BCRP preferentially targets hydrophobic, lipophilic compounds with planar aromatic systems. Numerous chemotherapeutic agents as well as antiviral drugs are exported by BCRP (Rabindran et al., 1998; Jonker et al., 2005; Pan et al., 2007; Giri et al., 2008; Chen et al., 2009; Agarwal et al., 2010). In addition, several endogenous substrates of BCRP have been identified. For example, BCRP was implicated in the maintainence of heme homeostasis under hypoxia by transporting out porphyrins (Jonker et al., 2002; Susanto et al., 2008). BCRP inhibitors exhibit similar structural characteristics and can competitively interfere with the substrate binding. Alternatively, some BCRP inhibitors can inhibit general ATPase activity (Mao and Unadkat, 2015). The mouse Bcrp transporter was shown to have overlapping substrate and inhibitor preference with the human BCRP isoform (Bakhsheshian et al., 2013). A list of example BCRP substrates and inhibitors is included in **Table 1**.

3.2. Clinical Importance of BCRP

Along with MDR1, the BCRP transporter is a key determinant of the efficacy and/or toxicity of the compounds. In human embryonic kidney 293 (HEK) cells expressing BCRP with a reduced-function polymorphism (C421A), there was significantly higher intracellular accumulation of BCRP substrates, Hoechst 33342 and an antidiabetic agent glyburide, compared to the HEK cells expressing wild-type BCRP (Bircsak et al., 2016). In Bcrp knockout pregnant mice, there were higher fetal concentrations as well as elevated fetal-to-maternal concentrations of glyburide compared to wild-type mice (Zhou et al., 2008). The importance of BCRP in regulating brain concentrations of chemicals has also been demonstrated in knockout mice. The brain concentration of dasatinib, a tyrosine kinase inhibitor, was significantly augmented in Mdr1a/1b/Bcrp triple knockout mice compared to Mdr1a/1b knockout mice, signifying the critical role of Bcrp transporter in limiting the penetration of dasatinib into the brain (Chen et al., 2009). Likewise, Bcrp knockout mice retain more Aβ, a pathological peptide in Alzheimer's Disease, in the brain compared to the wild-type mice, suggesting that BCRP also contributes to the clearance of Aβ (Do et al.,

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2012; Zhang et al., 2013). Collectively, this evidence points to BCRP as an important regulator of xenobiotic disposition and consequently tissue protection.

3.3. Transcriptional Regulation of BCRP

As observed with the *ABCB1* gene, several response elements are present in the *ABCG2* gene that enable recruitment of transcription factors and initiation of gene transcription. The *ABCG2* gene, located on chromosome 4q22, also has two promoters, upstream and downstream, that lead to different splicing in the 5' untranslated region (UTR) (Bailey-Dell et al., 2001; Campbell et al., 2011). Transcripts with different forms of the 5' UTR contribute to the tissue-specific expression of BCRP. The downstream promoter, located at 18 kb upstream of ATG-containing exon, produces the major transcripts (**Figure 2**). Therefore, the following discussion will focus on the downstream promoter. The *ABCG2* promoter, like the *ABCB1* promoter, lacks a TATA box but contains multiple binding sites for Sp1 and AP2 transcription factors in proximity to the TSS (at -49 and -50 bp upstream of the TSS). A potential initiator sequence is also found within the *ABCG2* promoter (CCACTGC). An AP1 binding site, CCAAT box, and additional Sp1 sites were also identified within -400 bp of the 5' flanking region. Analysis of the *ABCG2* promoter activity using deletion constructs revealed that the sequence up to -312 bp upstream from the TSS confers basal promoter activity. Furthermore, this study suggested the presence of positive regulatory element(s) between -1285 bp and -628 bp and negative regulatory element(s) between -628 bp and -312 bp upstream of the TSS (Bailey-Dell et al., 2001).

Several ligand-activated receptors have been implicated in the regulation of *ABCG2* transcription. Ee and colleagues identified a functional estrogen response element between -187 and -173 bp of the 5'-flanking region of *ABCG2* which was shown to interact with the estrogen receptor to mediate *ABCG2* gene activation (Ee et al., 2004). Also, the sequences from -1285 to -628 bp and from -243 to -115 bp in the 5'-flanking region were critical for progesterone-activated BCRP transcription, suggesting the presence of two putative progesterone response elements at these locations (Wang et al., 2008). A functional DRE recognized by AHR was also found near the *ABCG2* promoter (-194 to -190 bp) (Tan et al., 2010).

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Interestingly, the same study revealed that mouse *Abcg2* gene expression in mouse liver, mammary tissue, and intestinal carcinoma cell lines was not regulated by AHR activation. Indeed, the authors found that there were no conserved putative DREs between human *ABCG2* and mouse *Abcg2* genes. Additional response elements of xenobiotic-activated transcription factors including the constitutive androstane receptor and peroxisome proliferator-activated receptor alpha and gamma were also found at distal locations in the *ABCG2* gene (Szatmari et al., 2006; Benoki et al., 2012; Hoque et al., 2012; Hoque et al., 2015; Lin et al., 2017). Lastly, stress signals such as hypoxia and inflammation are also known to regulate BCRP expression (Krishnamurthy et al., 2004; Wang et al., 2010; Francois et al., 2017). In summary, the *ABCG2* gene, like *ABCB1*, contains binding sites for numerous transcription factors that can interact to regulate the rate and extent of transactivation.

4. EPIGENETIC REGULATION BY HISTONE ACETYLATION

4.1. Regulation of Histone Acetylation

Epigenetics is the regulation of gene expression that induces heritable changes without altering DNA sequence. This process of transcriptional modification has been implicated in the pathogenesis of various diseases including cancer and neurological disorders. There are three main mechanisms of epigenetic regulation: DNA methylation, small non-coding RNAs, and histone modifications. Modifications to histone proteins including acetylation, methylation, phosphorylation, and ubiquitination can either activate or suppress gene transcription by altering histone-DNA interactions and accessibility of the gene to transcription factors and transcriptional machinery (Allfrey et al., 1964; Pogo et al., 1966; Sung and Dixon, 1970; Lee et al., 1993; Li et al., 1993; Sun and Allis, 2002). The majority of histone modifications occur at the amino terminal tails of histones, which play a key role in stabilizing histone-DNA interactions (Allfrey et al., 1964; Sung and Dixon, 1970).

Histone acetylation is considered the most common and well-studied histone modification for the regulation of gene expression (Allfrey et al., 1964; Puerta et al., 1995; Kuo et al., 1998; Wang et al., 1998).

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This process occurs at lysine residues of histone amino terminal tails (Iwai et al., 1970; Zhang et al., 1998). Studies have established that histone acetylation enhances gene transcription by neutralizing the positive charge at the histone tails and decreasing histone affinity to the negatively-charged backbone of the DNA. Consequently, the DNA sequence becomes more accessible for interaction with transcription factors (Sung and Dixon, 1970; Cary et al., 1982; Hong et al., 1993). However, evidence also suggests that histone acetylation generates specific docking surfaces for transcriptional activators without significantly altering the electrostatic charges of histones (Lee et al., 1993).

Histone acetylation is a dynamic process that is regulated by specific enzymes. Histone acetyltransferases or HATs facilitate the addition of acetyl groups to lysine residues on histone tails to reduce their overall positive charge (Kuo et al., 1996; Wang et al., 1998). This results in the loss of tight electrostatic interactions between histones and DNA, transforming DNA into an open and relaxed state (Sung and Dixon, 1970; Cary et al., 1982; Hong et al., 1993). This conformation makes DNA more available to transcription factors and subsequently increases gene expression (Lee et al., 1993; Kuo et al., 1998; Wang et al., 1998). Human HATs are classified into three major subfamilies based on sequence similarity: Gcn5/PCAF, MYST, and p300/CBP (Kuo et al., 1996; Ogryzko et al., 1996; Yang et al., 1996; Wang et al., 1997; Clarke et al., 1999; Iizuka and Stillman, 1999). These subfamilies are distinct from each other in structural properties, substrate binding, and catalytic strategies.

Histone deacetylases (HDACs) hydrolyze and remove acetyl groups on modified histone tails to reestablish tight interaction between histones and DNA (Inoue and Fujimoto, 1969; Hirschhorn et al., 1992; Lopez-Rodas et al., 1993; Kuo et al., 1996; Taunton et al., 1996; Kuo et al., 1998). DNA becomes tightly wrapped around histones and chromatin resumes a dense structure to suppress gene expression. Even though these enzymes are called “histone” deacetylases, they also possess non-histone targets such as p53, α-tubulin, and heat shock proteins that are involved in a variety of cellular processes (Juan et al., 2000; Vaziri et al., 2001; Hubbert et al., 2002; Bali et al., 2005). In fact, a phylogenetic study suggests that evolution of HDAC enzymes was earlier than that of histone proteins, therefore implying the possibility that the primary targets of HDAC enzymes are non-histone proteins (Gregoretti et al., 2004). Eighteen

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groups of HDACs are divided into different families and classes based on sequence and functional similarity (Rundlett et al., 1996; Taunton et al., 1996; Grozinger et al., 1999; Gregoretti et al., 2004). Representative members of each class of HDAC are summarized in **Table 2**. A "classical" HDAC family, which requires zinc for its activity, includes classes I, II, and IV (Finnin et al., 1999; de Ruijter et al., 2003). Class III HDACs belong to a zinc-independent and nicotinamide adenine dinucleotide (NAD)-dependent sirtuin enzyme family (Imai et al., 2000; North and Verdin, 2004).

Class I includes HDACs 1 and 2, which are predominantly located in the nucleus, and HDACs 3 and 8, which have been shown to shuttle between the nucleus and cytoplasm (Bjerling et al., 2002; Johnson et al., 2002; Yang et al., 2002). Class I HDACs have intrinsic enzymatic activity to deacetylate all four types of core histones but to varying extents (Hassig et al., 1998; Hu et al., 2000; Johnson et al., 2002). Studies showed that these enzymes are present in different protein complexes where they exert maximal enzymatic function and possess low activity when isolated alone without associated proteins (Heinzel et al., 1997; Laherty et al., 1997; Zhang et al., 1999; Wen et al., 2000). Class II can be further divided into class IIa, which includes HDACs 4, 5, 7 and 9, and class IIb, which includes HDACs 6 and 10. Class IIa HDACs are capable of shuttling between the nucleus and cytoplasm (Grozinger and Schreiber, 2000; Kao et al., 2000; McKinsey et al., 2000a; McKinsey et al., 2000b; Fischle et al., 2001; Wang and Yang, 2001; Petrie et al., 2003; Harrison et al., 2010; Sugo et al., 2010). In contrast, HDAC6 functions primarily in the cytoplasm to regulate tubulin acetylation (Verdel et al., 2000; Hubbert et al., 2002). HDAC10, a relatively unknown HDAC that is found in both the nucleus and cytoplasm, was shown to play roles in transcriptional repression and regulation of cell cycle (Guardiola and Yao, 2002; Kao et al., 2002; Li et al., 2015). Early results suggest that class IIa HDACs do not exhibit intrinsic deacetylase capability on histones but instead carry out transcriptional repression via interaction with HDAC3 proteins (Wen et al., 2000; Fischle et al., 2001; Fischle et al., 2002). However, findings have indicated that these HDAC enzymes do have measurable deacetylase activities that are restricted to certain sets of yet undefined substrates (Lahm et al., 2007; Jones et al., 2008). Class IV contains a sole member, HDAC11, that is structurally different from both class I and II HDACs (Gao et al., 2002). The function of HDAC11 is the least studied in the "classical"

HDAC family. Class III HDACs includes seven structurally distinct NAD-dependent sirtuin (SIRT) enzymes which have distinct subcellular localizations as listed in **Table 2** (North et al., 2003; Michishita et al., 2005; Haigis et al., 2006; Mostoslavsky et al., 2006; Ahuja et al., 2007; Inoue et al., 2007; Scher et al., 2007; Tanno et al., 2007; Nakamura et al., 2008; Grob et al., 2009; Nakagawa et al., 2009; Nasrin et al., 2010; Iwahara et al., 2012; Kiran et al., 2013). SIRTs can perform two enzymatic activities, deacetylase and mono ADP-ribosyltransferase, whose activities are closely linked to each other (Frye, 1999; Tanny et al., 1999; Imai et al., 2000; Landry et al., 2000a; Landry et al., 2000b). These enzymes play roles in various important biological processes including the regulation of cell cycle, apoptosis, insulin secretion, and aging (Vaziri et al., 2001; Dryden et al., 2003; Howitz et al., 2003; Cohen et al., 2004; Motta et al., 2004; Moynihan et al., 2005).

Class I HDACs are ubiquitously expressed, except for HDAC8 which is more selectively found in smooth muscle cells (Caron et al., 2001; Waltregny et al., 2004). HDACs 1 through 3 are thought to be widely distributed throughout different regions of the brain (Uhlen et al., 2005; Broide et al., 2007; Berglund et al., 2008; Lucio-Eterovic et al., 2008; Ponten et al., 2008; Anderson et al., 2015; Uhlen et al., 2015; Thul et al., 2017; Uhlen et al., 2017). Class II HDACs are also distributed widely but to varying extents in different tissues. For example, class IIa HDACs are more predominantly found in muscle and heart while class IIb shows greater expression in liver and kidney (Fischle et al., 1999; Grozinger et al., 1999; Wang et al., 1999; Caron et al., 2001; Dressel et al., 2001; Kao et al., 2002). HDACs 4 and 5 are most highly expressed in the brain, and HDAC6 is abundantly found in cerebellar Purkinje cells (Uhlen et al., 2005; Broide et al., 2007; Southwood et al., 2007; Berglund et al., 2008; Ponten et al., 2008; Uhlen et al., 2010; Uhlen et al., 2015; Thul et al., 2017; Uhlen et al., 2017). HDAC11 was detected across a number of tissues including brain, kidney, testes, and skeletal muscle (Gao et al., 2002; Broide et al., 2007). Each class III SIRT enzyme displays a distinct tissue expression profile (Afshar and Murnane, 1999; Frye, 1999; Onyango et al., 2002). Certain HDACs including HDACs 4, 8, and 9 appear to be enriched more in tumor tissues than in normal somatic tissues; however, HDACs overall are similarly expressed between normal

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and tumor tissues, although the level can be largely variable between different tumor types (Caron et al., 2001; de Ruijter et al., 2003).

4.2. Modulators of HDAC Activity: HDAC Inhibitors

Due to the critical roles of HATs and HDACs in regulating transcription, the balance between these two classes of enzymes is tightly controlled. Imbalance in the activities of HATs and HDACs can lead to aberrant gene expression and dysregulation of key cellular processes including cell proliferation as reviewed in numerous papers (Sommer et al., 1997; Giles et al., 1998; Kruhlak et al., 2001; Timmermann et al., 2001; Lehrmann et al., 2002; Groth et al., 2007; Haberland et al., 2009). This can consequently contribute to the pathogenesis of diseases such as cancer (Petrij et al., 1995; Cress and Seto, 2000; Choi et al., 2001; Murata et al., 2001; Seligson et al., 2005; Haberland et al., 2009). Therefore, these histone-modifying enzymes have been identified as attractive therapeutic targets. Inhibitors of HATs and HDACs have been developed and actively investigated for their ability to reverse disease-associated epigenetic modifications. In particular, HDAC inhibitors have been extensively studied as potential therapy for cancer and neurological and psychiatric diseases (Hockly et al., 2003; Simonini et al., 2006; Tsankova et al., 2006; Vecsey et al., 2007; Coiffier et al., 2012; Harrison et al., 2015; Schmitt et al., 2016; Zhou et al., 2018). Indeed, some HDAC inhibitors are already FDA-approved for treatment of lymphoma and epilepsy and described below (USFDA, 1978; Koch-Weser and Browne, 1980; AbbVie, 1983; Merck & Co., 2006; Thompson, 2006; Celgene Corporation, 2009; Yang, 2011).

HDAC inhibitors are a group of structurally diverse compounds that block the activities of HDAC enzymes with varying selectivity and potency. Largely, these compounds can be divided into two groups: classical HDAC inhibitors that target classical, zinc-dependent HDAC enzymes, and SIRT inhibitors that act on class III SIRT, NAD-dependent enzymes. SIRT inhibitors have been less extensively investigated than classical HDAC inhibitors, and the interactions between SIRT inhibitors and efflux transporters have not been identified yet. Thus, the remainder of this review will focus on classical HDAC inhibitors, generally referred to as “HDAC inhibitors”. HDAC inhibitors inactivate HDAC enzymes by competitively

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inhibiting the binding of zinc within active sites (Finnin et al., 1999). Inhibition of HDACs enhances acetylation of histones and binding of transcription factors to up-regulate the expression of multiple genes (Riggs et al., 1977; Vidali et al., 1978; Yoshida et al., 1990; Van Lint et al., 1996; Butler et al., 2000; Glaser et al., 2003). In particular, HDAC inhibitors have been shown to up-regulate various tumor suppressor and proapoptotic genes to prevent cancer cell proliferation (Davis et al., 2000; Kim et al., 2001; Peart et al., 2003; Nakata et al., 2004). Consequently, pharmacological inhibitors of HDACs were initially investigated for their potential as anticancer drugs. This research led to the approval of HDAC inhibitors for the treatment of lymphomas, namely, romidepsin (Istodax®), suberoylanilide hydroxamic acid or vorinostat (SAHA, Zolinza®), belinostat (Beliodaq®), and panobinostat (Farydak®) for multiple myeloma (Merck & Co., 2006; Thompson, 2006; Celgene Corporation, 2009; Yang, 2011; Poole, 2014; Spectrum Pharmaceuticals, 2014; Lee et al., 2015; Novartis Pharmaceuticals Corporation, 2015).

The disruptive effects of HDAC inhibitors can be reversed and normal cells are more capable than cancer cells to repair or compensate for the molecular changes induced by HDAC inhibitors (McKnight et al., 1980; Richon et al., 1998; Deroanne et al., 2002; Xu et al., 2007). Therefore, HDAC inhibitors have relatively less pharmacological impact on normal tissues (Burgess et al., 2004; Insinga et al., 2005; Ungerstedt et al., 2005; Xu et al., 2007). Indeed, mice with a genetic deletion of a single isoform HDAC may not exhibit significant phenotypic or pathological changes, possibly due to compensation by other HDAC enzymes (Montgomery et al., 2007; Zhang et al., 2008). Yet, there are still concerns for undesirable effects of HDAC inhibitors because these compounds are nonspecific, affecting multiple HDACs at the same time (Khan et al., 2008; Bradner et al., 2010). For example, SAHA is a pan-HDAC inhibitor which targets both class I and II HDAC enzymes. It is challenging to develop a highly selective HDAC inhibitor because different isoforms of HDAC enzymes, especially those in the same class, share highly homologous active sites and catalytic mechanisms (Richon et al., 1998; Miller et al., 2003). More extensive investigation regarding the crystalline structures as well as enzymatic mechanisms of HDACs identified few differences between various isoforms, and subsequently led to the development of more specific inhibitors that selectively act on only two or three isoforms (Vannini et al., 2004; Wang et al., 2005; Guo et al., 2007;

Ficner, 2009; Burli et al., 2013). For example, romidepsin is a class I HDAC inhibitor that is particularly selective for HDACs 1 and 2 (Furumai et al., 2002). Such difference in target specificity may contribute to the potency, relative toxicity, and/or off-target effects of HDAC inhibitors, as well as particular molecular changes elicited by these agents.

4.2.1. Classification of HDAC Inhibitors

HDAC inhibitors can be classified based on the properties of their core chemical structures (Miller et al., 2003). The structural characteristics that divide HDAC inhibitors into different classes are outlined in **Table 3**. Structural properties of HDAC inhibitors are important determinants of their selectivity as well as potency. The basic pharmacophore of classical HDAC inhibitors generally consists of three main elements: (1) the zinc-binding domain that contains a functional group binding to the active site of HDACs, (2) surface recognition domain that allows for effective interaction of inhibitors with the catalytic pocket of enzymes, and a (3) chain linker domain (Miller et al., 2003). Variation in this core structure affects the inhibitory mechanisms and efficacy of HDAC inhibitors.

Hydroxamates comprise the largest class of HDAC inhibitors and include three FDA-approved HDAC inhibitors, SAHA, belinostat, and panobinostat (Richon et al., 1998; Plumb et al., 2003; Qian et al., 2006; Thompson, 2006; Poole, 2014; Laubach et al., 2015; Lee et al., 2015). The primary functional group of these inhibitors is a hydroxamic acid, which directly interacts with the zinc ion to inhibit the catalytic action of HDAC enzymes. The chain linker domain in hydroxamates can be linear or cyclic (Yoshida et al., 1990; Richon et al., 1998; Miller et al., 2003). They are among the most potent inhibitors. The potency of hydroxamates, as assessed by the IC_{50} on purified HDACs, is in the nanomolar to micromolar range, and each individual compound in this class possesses different ranges of potency and selectivity (Yoshida et al., 1990; Richon et al., 1998; Furumai et al., 2002; Plumb et al., 2003). Generally, hydroxamates are pan-HDAC inhibitors that target both class I and II HDAC enzymes. Trichostatin A (TSA) and SAHA exhibit greater potency to class I and IIb HDACs compared to class IIa HDACs (Khan et al., 2008; Bradner et al., 2010; Kilgore et al., 2010). Belinostat and panobinostat are considered to be substrates (but not inhibitors)

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of MDR1 whereas SAHA is generally not considered to be either a substrate or an inhibitor of MDR1 (Merck & Co., 2006; Spectrum Pharmaceuticals, 2014; Novartis Pharmaceuticals Corporation, 2015).

Cyclic peptides are also highly potent HDAC inhibitors that contain functional groups directly interacting with the zinc ion in the catalytic site. These inhibitors are characterized by a surface recognition domain that contains a macrocycle with hydrophobic amino acids (Kijima et al., 1993; Darkin-Rattray et al., 1996; Nakajima et al., 1998; Furumai et al., 2002; Miller et al., 2003). Cyclic peptides are generally known as class I HDAC inhibitors but there is a large structural dissimilarity within this class of inhibitors, contributing to variable selectivity among them. For example, romidepsin is more selective towards HDACs 1 and 2 while apicidin is more potent against HDACs 2 and 3 (Furumai et al., 2002; Matsuyama et al., 2002; Khan et al., 2008; Bradner et al., 2010). Romidepsin is also recognized as a substrate of MDR1 (Celgene Corporation, 2009).

In contrast to the previous two classes of HDAC inhibitors, shorty chain fatty acids (SCFAs) are relatively weak inhibitors with IC_{50} concentrations using purified HDAC enzymes largely in the millimolar range of concentrations (Boffa et al., 1978; Candido et al., 1978; Gottlicher et al., 2001; Phiel et al., 2001; Khan et al., 2008). This relatively weak potency is attributed to suboptimal structural characteristics of SCFAs. First, the inhibitory action of these compounds does not involve an effective interaction with the zinc ion, which is a central component of HDAC activity (Lu et al., 2004). In addition, SCFAs do not possess surface recognition domains that enable tight binding of HDAC inhibitors to target enzymes (Miller et al., 2003). Together, these properties result in the weak potency of SCFAs. However, unlike hydroxamates and cyclic peptides which can have limited access to brain, SCFAs exhibit good penetration into the brain, making them attractive therapeutic options for brain diseases (Cornford et al., 1985; Phiel et al., 2001; Shin et al., 2011; Hanson et al., 2013). Indeed, valproic acid (VPA) is a FDA-approved SCFA HDAC inhibitor indicated for epilepsy and psychiatric mania (Lewis, 1978; Brown, 1979; Guay, 1995). VPA is not reported to be a substrate or an inhibitor of MDR1 (AbbVie, 1983).

Benzamides including MS-275 (entinostat) are also brain-penetrant HDAC inhibitors that are more specific and potent than SCFAs (Suzuki et al., 1999; Park et al., 2004; Eyupoglu et al., 2006; Simonini et

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al., 2006; Boissinot et al., 2012). A key structural feature of these compounds is a 2' amino/hydroxyl group in benzanilide (Suzuki et al., 1999; Miller et al., 2003). Benzamides selectively target class I HDACs, and cross the BBB effectively (Hu et al., 2003; Eyupoglu et al., 2006; Simonini et al., 2006; Chou et al., 2008; Khan et al., 2008; Boissinot et al., 2012). Also, clinical trials showed that MS-275 had a much longer half-life (over 30 hours) than other classes of HDAC inhibitors (Ryan et al., 2005; Acharya et al., 2006; Kummar et al., 2007). However, benzamide HDAC inhibitors are generally less potent than hydroxamates or cyclic peptides (Park et al., 2004; Beckers et al., 2007; Boissinot et al., 2012).

4.2.2. Clinical Utility of HDAC Inhibitors

Due to their ability to modify the expression of genes and proteins, HDAC inhibitors have been utilized as drugs to correct aberrant molecular pathways in various disease such as cancer and neurological disorders. Three HDAC inhibitors, SAHA, romidepsin, and belinostat, have been approved by the FDA in 2006, 2009, and 2014, respectively, for treatment of T-cell lymphomas (Merck & Co., 2006; Thompson, 2006; Celgene Corporation, 2009; Yang, 2011; Poole, 2014; Spectrum Pharmaceuticals, 2014; Lee et al., 2015). Panobinostat was approved in 2015 for treatment of multiple myeloma (Novartis Pharmaceuticals Corporation, 2015). HDAC inhibitors induce antitumor effects by: (1) inducing the expression of tumor suppressors including p53 and p21, promoting cell cycle arrest, and inhibiting cell proliferation (Davis et al., 2000; Richon et al., 2000; Kim et al., 2001); (2) activating extrinsic and intrinsic apoptosis by upregulating death receptors and proapoptotic proteins (Kawagoe et al., 2002; Nakata et al., 2004; Insinga et al., 2005); and (3) inhibiting angiogenesis through induction of anti-angiogenic genes and repression of pro-angiogenic genes (Kim et al., 2001; Deroanne et al., 2002; Kwon et al., 2002). Clinical studies are being actively performed to test the effects of HDAC inhibitors in other types of cancer including glioblastoma (Galanis et al., 2009; Bailey et al., 2016; Kusaczuk et al., 2016; Choi et al., 2017; Barneh et al., 2018; Monga et al., 2018).

Studies also indicate the therapeutic potential of HDAC inhibitors in a wide array of neurological diseases including stroke, Parkinson's Disease, Alzheimer's Disease, and Huntington's Disease as well as

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psychiatric diseases including depression and schizophrenia (Hockly et al., 2003; Chen et al., 2006; Faraco et al., 2006; Kontopoulos et al., 2006; Simonini et al., 2006; Tsankova et al., 2006; Kim et al., 2007; Fontan-Lozano et al., 2008; Qing et al., 2008; Suzuki et al., 2009; Xuan et al., 2015). As discussed in the previous section, VPA is FDA-approved to treat epilepsy and psychiatric mania (Lewis, 1978; Brown, 1979; Guay, 1995). There are different pathways by which HDAC inhibitors can ameliorate these brain diseases: (1) eliciting anti-inflammatory responses by decreasing proinflammatory mediators including IL-6, COX-2, and TNF-α (Qi et al., 2004; Sinn et al., 2007); (2) reducing the synthesis or enhancing the degradation of neurotoxic proteins and factors, such as Aβ and α-synuclein (Kawaguchi et al., 2003; Kontopoulos et al., 2006; Qing et al., 2008; Xuan et al., 2015); and (3) exerting neuroprotection via induction of neurotrophic factors (Chen et al., 2006; Wu et al., 2008). Because of their selective inhibition of class I HDACs and suitable brain penetration, benzamide HDAC inhibitors are being actively investigated as treatments for central nervous system disorders (Eyupoglu et al., 2006; Simonini et al., 2006; Covington et al., 2009; Zhang and Schluesener, 2013). In addition to these disease states, there are other conditions such as endometriosis, somatic cell nuclear transfer, inflammation, and pulmonary disorders where HDAC inhibitors could be useful, indicating a broad applicability of these compounds across clinical settings (Plumb et al., 2003; Rybouchkin et al., 2006; Wu et al., 2007).

5. HISTONE ACETYLATION IN THE REGULATION OF EFFLUX TRANSPORTERS

One challenge for the effective use of HDAC inhibitors to treat cancer has been their ability to alter the expression and/or activity of ABC efflux transporters, which are often the main mediators of multidrug resistance in tumors. In 1989, Mickley and colleagues showed that sodium butyrate up-regulated both the mRNA and protein expression of MDR1 in SW620 and HCT-15 colon carcinoma cells (Mickley et al., 1989). Increased MDR1 expression in HCT-15 cells was accompanied by enhanced efflux of MDR1-transported chemotherapeutic drugs, highlighting the clinical importance of this observation. Further studies were performed in an array of cancer cell lines to evaluate the effects of various HDAC inhibitors on the expression and activity of MDR1 as well as other ABC transporters including BCRP. In most cell

lines tested, HDAC inhibitors led to an up-regulation of transporter expression, though at varying concentrations and time points. Also, the same chemical exerted differential effects depending upon the cell type being tested. Subsequent studies explored the mechanisms underlying the induction of efflux transporters by HDAC inhibitors. The results of mechanistic studies point to roles for histone acetylation in regulating ABC transporters. Currently, there are limited findings on the regulation of transporters by HDAC inhibitors in non-cancerous cells.

5.1. Effects of HDAC Inhibitors on the MDR1 Transporter

The effects of HDAC inhibitors on the regulation of the MDR1 transporter in over sixty different cancer and non-cancer cell lines are summarized in **Table 4**. Overall, the study results indicate that HDAC inhibitors largely up-regulate the expression and/or activity of the MDR1, but often in a chemical-specific and a cell type-specific manner. HDAC inhibitors exert their ability to up-regulate MDR1 at concentration ranges that correlate with HDAC IC_{50} ranges (**Table 3**) as determined using purified HDAC activity assays (Boffa et al., 1978; Gottlicher et al., 2001; Furumai et al., 2002; Miller et al., 2003).

5.1.1. Hydroxamic Acids

Trichostatin A (TSA), a hydroxamate HDAC inhibitor, increased mRNA expression of MDR1 at concentrations ranging from 0.132μM to 5μM in a wide array of human cell lines including cancerous cells of colon, stomach, pancreas, prostate, lung, breast, cervix, ovary, bone marrow, and lymphoid organs. In RWP-1 and PANC-1 pancreatic cancer cells, 1μM TSA induced MDR1 mRNA as early as 3 h after treatment while the induction was not observed until later time points in other pancreatic cancer cells such as IMIM-PC-1, IMIM-PC-2, and HS766T (Balaguer et al., 2012). In colon cancer cells, TSA-mediated induction of MDR1 mRNA was observed starting at 6 h after the treatment, but at lower concentrations (0.1μM to 0.5μM) than in pancreatic cancer cells (Jin and Scotto, 1998; Baker et al., 2005; Gomez-Martinez et al., 2007; Lee et al., 2008; Wang et al., 2019).

In other human cancer cells, TSA altered MDR1 mRNA levels generally by 24 h although there were some exceptions. For example, TSA caused more than a three-fold increase in MDR1 mRNA at 0.33μM in HeLa cervical adenocarcinoma cells while it did not alter MDR1 mRNA in HeLa contaminant carcinoma KB cells even at 10-fold higher concentration of 3μM (Kim et al., 2008; Kim et al., 2009; Huo et al., 2010; Kim et al., 2011). In BeWo and JAR choriocarcinoma cells, which are *in vitro* models of human placental trophoblasts, TSA exhibited a dose-dependent and time-dependent regulation of MDR1 expression. TSA up-regulated MDR1 by 48 h at lower concentrations (0.5μM and 1μM) but by 24 h when higher concentrations (3μM and 5μM) were used. The level of MDR1 mRNA and protein returned to the baseline by 72 h of treatment with TSA in JAR cells, denoting tight temporal regulation of this transporter (Duan et al., 2017a). Time-dependent reversal of MDR1 induction was also seen in human brain microvascular endothelial (hCMEC/D3) cells, an *in vitro* model of the human BBB, which is a highly regulated structure in the body. In hCMEC/D3 cells, TSA caused approximately two-fold increase in MDR1 mRNA at 12 h, which was largely attenuated by 24 h (You et al., 2019b).

Induction of MDR1 mRNA by TSA translates into increased protein expression and/or enhanced transporter activity only in certain cell lines. For example, TSA increased MDR1 mRNA without affecting its protein or function in human colon and pancreatic cancer cell lines while both MDR1 mRNA induction and enhanced transport of the substrate doxorubicin were observed in MCF-7 breast cancer cells treated with TSA (Gomez-Martinez et al., 2007; Balaguer et al., 2012; Toth et al., 2012). The study by Gomez-Martinez (2007) et al suggested that the differential up-regulation of MDR1 protein by TSA could be due to the difference in MDR1 mRNA stability, which consequently affects the translation of MDR1 mRNA into protein (Gomez-Martinez et al., 2007). Therefore, we can infer that varying MDR1 mRNA products in different cell lines may contribute to cell type-specific responses to TSA. Interestingly, conflicting results were observed with hCMEC/D3 brain endothelial cells. Noack and the colleagues showed that 0.33μM TSA moderately altered MDR1 function, but not the protein expression, through increasing the cell-to-cell transfer of MDR1 protein (Noack et al., 2016). MDR1 intercellular transfer has been implicated in the

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acquisition of multidrug resistance in tumor cells (Levchenko et al., 2005). By contrast, a recent study demonstrated the protein expression of MDR1 in hCMEC/D3 cells was significant increased after 24 h of treatment with 0.25μM TSA, which was noted as the highest non-toxic concentration (You et al., 2019b).

Suberyolanilide hydroxamic acid (SAHA, Vorinostat, Zolinza®), an FDA-approved hydroxamate HDAC inhibitor for cutaneous and peripheral T cell lymphoma (Merck & Co., 2006), also exerted an ability to regulate efflux transporter expression in diverse types of human cells including both cancerous and normal cells. In most cells tested, SAHA induced MDR1 mRNA and protein, but like TSA, SAHA also showed cell type-specific responses. For example, 0.2μM of SAHA was sufficient to up-regulate MDR1 in HCT-8 ileocecal colorectal adenocarcinoma cells by 48 h while HCT-116 colorectal carcinoma cells required a higher concentration to achieve similar results (Xu et al., 2012). Like TSA, SAHA induced MDR1 mRNA in HeLa cells, but not in KB cells (Kim et al., 2009; Kim et al., 2011). The average concentration at which SAHA up-regulated MDR1 was slightly higher than TSA, as expected based on their relative IC_{50} concentrations obtained from purified HDAC enzyme inhibition studies. The ability to induce transporter expression was seen as early as 8 h post-treatment in K562 chronic myelogenous leukemia (CML) cells, whereas longer exposures to SAHA enhanced MDR1 expression in other cell lines (Xiao et al., 2005; Hauswald et al., 2009). Similar to TSA, SAHA affects MDR1 expression in BeWo and JAR choriocarcinoma cells in a dose- and time-dependent manner (Duan et al., 2017a). Lower concentrations of SAHA (0.5μM and 1μM) could not induce MDR1 in BeWo cells even after 72 h of exposure while higher concentrations (3 and 5μM) caused up-regulation by 24 – 48 h. In JAR cells, SAHA was able to induce MDR1 as early as 24 h post-exposure at 0.5, 1, 3, and 5μM concentrations. However, as seen with TSA, SAHA-mediated MDR1 induction in JAR cells was absent at 72 h of treatment. Likewise, MDR1 mRNA in hCMEC/D3 cells was shown to be significantly increased as early as 6 h following exposure to 10μM SAHA, and then returned to the baseline level by 24 h. In the same cells, the level of MDR1 protein, which has a longer half-life than MDR1 mRNA, remained elevated until 36 h after SAHA

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treatment. Such protein up-regulation translated into enhanced functional activity of MDR1, as indicated by reduced intracellular accumulation of Rhodamine 123, a fluorescent MDR1 substrate (You et al., 2019b).

The ability of SAHA to regulate MDR1 expression was also observed in a clinical study. Administration of escalating doses of SAHA for 4 to 7 days in patients (n=8 paired samples) with relapsed or refractory acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), secondary AML, or CML resulted in notable MDR1 mRNA induction in the bone marrow or peripheral blood mononuclear cells of three patients (p-values ranging from <0.001 to 0.057). Interestingly, one patient, who had a significantly higher baseline MDR1 mRNA expression, experienced a significant reduction in MDR1 mRNA by SAHA treatment. Differential responses to SAHA may be due to an altered molecular environment in this patient with more resistant disease, as discussed in a later section of this review. Alternatively, this result suggests that HDAC inhibition does not always favor MDR1 up-regulation and that baseline expression of MDR1 may determine the manner by which the HDAC inhibitor affects transcription of the *ABCB1* gene. Unlike changes in mRNA, no significant changes in protein level or activity of MDR1 were observed in the same patient group (Gojo et al., 2013). Future clinical studies with a larger number of subjects are desired to more clearly elucidate the MDR1 regulatory effects of SAHA in humans.

Likewise, belinostat (Beleodaq®), also FDA-approved for lymphoma (Spectrum Pharmaceuticals, 2014), caused an increase in MDR1 mRNA in bone marrow aspirate samples of AML patients receiving azacytidine (Odenike et al., 2015). In contrast, belinostat decreased the protein expression of MDR1 in PEER human T-cell ALL cells after 48 h of treatment at 6μM concentration (Valdez et al., 2016). Few studies have evaluated the *in vitro* effects of belinostat on transporter regulation, and further studies are necessary to better elucidate the ability of belinostat to modulate MDR1 expression. Panobinostat (Farydak®), the most recently approved HDAC inhibitor indicated for multiple myeloma (Novartis Pharmaceuticals Corporation, 2015), has also been assessed for its ability to modulate MDR1 in several human cancer cells including SF295 glioblastoma cells (To et al., 2011; Valdez et al., 2016). Panobinostat is more potent in its ability to up-regulate MDR1 compared to other hydroxamate-type inhibitors with

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induction observed at nanomolar concentrations of panobinostat (15nM to 150nM) over a period of 9 to 48 h after treatment (To et al., 2011; Valdez et al., 2016). In PEER leukemia cells, up-regulation of MDR1 expression was reflected in enhanced activity as indicated by increased efflux of 3, 3'-diethyloxacarbocyanine iodide and daunorubicin, two known substrates of MDR1 (Valdez et al., 2016).

Overall, the studies reviewed in this section support that hydroxamate HDAC inhibitors could alter both the expression and the function of MDR1 in various cells, though at varying concentrations and time points. Each cell type may possess different genetic and transcriptomic characteristics or relative expression and activity of various HDAC isoforms, which can also affect the activity of the HDAC inhibitors. Evidence for potential *in vivo* modulation of MDR1 by hydroxamate HDAC inhibitors has also been presented. Together, these data indicate that the administration of hydroxamate HDAC inhibitors, several of which are clinically used, can lead to altered function of MDR1 transporter which regulates the trafficking of numerous drugs.

5.1.2. Short Chain Fatty Acids

Short chain fatty acids (SCFAs) such as VPA and butyrates, which are less potent HDAC inhibitors, generally require millimolar concentrations to induce MDR1. In human leukemia cells, SCFAs enhanced both the expression and functional activity of MDR1 as early as at 24 h at concentrations ranging from 0.5mM to 6mM (Eyal et al., 2006; Hauswald et al., 2009; Fuchs et al., 2010). Also, in different lung cancer cell lines, 3mM sodium butyrate significantly increased both mRNA and protein levels of MDR1 (Zhao et al., 2018). Similar to TSA and SAHA, VPA (0.3mM to 5mM) was able to modulate MDR1 expression and/or function in hCMEC/D3 brain endothelial cells (Noack et al., 2016; You et al., 2019b). However, 0.25mM sodium butyrate, which was the highest nontoxic concentration in hCMEC/D3 cells, did not significantly alter the mRNA or protein expression of MDR1 in those cells. Yet, higher concentrations of sodium butyrate (0.5mM to 3mM) in other cancer cell lines including thyroid and colon cancer cells significanty increased the expression and/or activity of MDR1, suggesting that the modulatory effect on MDR1 by sodium butyrate in hCMEC/D3 cells is likely concentration-dependent (Bates et al., 1992;

Frommel et al., 1993; Morrow et al., 1994; Massart et al., 2005; Pasvanis et al., 2012; Yan et al., 2017; Zhao et al., 2018). But overall, the effects of SCFAs were roughly similar across different cell lines tested. Furthermore, SCFAs were shown to induce Mdr1 mRNA in livers of male Sprague-Dawley rats following intraperitoneal doses of VPA and butyrate for 7 days (Eyal et al., 2006). Likewise, 7-day intraperitoneal treatment with VPA, a brain-penetrable HDAC inhibitor, significantly up-regulated the Mdr1 protein in the striatum of C57BL/6 mice along with levels of acetylated histone H3K9/14 (You et al., 2019a). Such *in vivo* data extend the *in vitro* findings and suggest that SCFA HDAC inhibitors can alter MDR1 expression in normal healthy tissues as well as cancer cell lines.

5.1.3. Cyclic Peptides

Cyclic peptides, including apicidin and romidepsin, are highly potent regulators of MDR1 across diverse *in vitro* and *in vivo* systems. The highly selective nature of cyclic peptide HDAC inhibitors to preferentially target only a couple isoforms of HDACs may contribute to the potency of these inhibitors. Apicidin increased the mRNA and/or protein expression of MDR1 in DLD-1 human colon cancer cells, hCMEC/D3 human microvascular endothelial cells, as well as HeLa and SiHa cervical cancer cells at concentrations ranging from 0.1μM to 3μM (Kim et al., 2008; Kim et al., 2009; You et al., 2019b). In hCMEC/D3 cells, apicidin even led to an enhanced functionality of the MDR1 transporter, as measured by the extent of accumulation of Rhodamine 123, a MDR1 substrate (You et al., 2019b). However, apicicidin did not alter MDR1 levels in KB cells or A172 and U87 glioblastoma cells, displaying selectivity in transporter regulation (Kim et al., 2008; Kim et al., 2009; Kim et al., 2011). By comparison, romidepsin up-regulated both MDR1 expression and activity at concentrations as low as 1.85nM in SW620 human colon cancer cells (Robey et al., 2006; To et al., 2008; To et al., 2011). In S1 colon cancer cells, the inhibitor also caused induction of MDR1 mRNA but at a higher concentration (9.25nM) (To et al., 2008). Similarly, romidepsin increased the expression and activity of MDR1 in kidney cancer cell lines, but only in a subset (Robey et al., 2006). Furthermore, unlike apicidin, romidepsin did not affect the MDR1 in hCMEC/D3 cells but induced the mRNA expression of MDR1 in SF295 human glioblastoma cells (To et al., 2008; To et al.,

2011; You et al., 2019b). These results suggest that romidepsin also regulates the MDR1 transporter in a manner quite specific to each cell type.

The up-regulatory effects of cyclic peptides on MDR1 regulation were also observed *in vivo*. Our recent study showed that apicidin is capable of altering the transport properties of the normal mouse brain (alongside increased levels of acetylated histone H3K9/14 protein), but in a region-specific manner (You et al., 2019a). A 7-day intraperitoneal injection of apicidin in C57BL/6 mice moderately, yet significantly, increased Mdr1 protein expression in the striatum, but not in the cortex, the midbrain, or the hippocampus. Differences in baseline Mdr1 expression across the brain regions may have contributed to selective effects of apicidin. Alternatively, local uptake of apicidin may also differ and contribute to the region-specific pharmacodynamic effects. The extraction of apicidin from the blood may differ between brain regions and in turn affect its pharmacological activity as noted by differences in the extent of histone acetylation, an indicator of HDAC inhibition. Finally, it is important to note that there are multiple cell types in the brain (endothelial cells, astrocytes, neurons or microglia), and that apicidin-mediated Mdr1 up-regulation could be specific to a certain cell type that may be differentially populated across brain regions.

The ability of romidepsin to regulate MDR1 expression has been assessed in clinical specimens. For example, romidepsin increased MDR1 mRNA in normal peripheral blood mononuclear cells of patients with lymphoma or leukemia up to 4 h after treatment. In contrast, induction of MDR1 mRNA by romidepsin lasted for 24 to 48 h post-dose in tumor samples from patients with lymphomas (Robey et al., 2006; Odenike et al., 2008; Bates et al., 2010). The AUC level of romidepsin (2.8μM*h) in patients after 4-hr infusion at a 14mg/m^2 dose was higher than the maximum plasma concentration (0.7μM) suggesting that the tissue exposure of romidepsin may be higher than the concentration measured in the circulation (Celgene Corporation, 2009). A potentially higher level of romidepsin in tissues may contribute to a longer upregulatory effect of romidepsin on MDR1 mRNA.

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Collectively, the data presented in this section suggest that the ability of cyclic peptide HDAC inhibitors to regulate MDR1 is selective according to certain cell types, but that this class of drugs is much more potent than other classes of HDAC inhibitors.

5.1.4. Divergent Responses in Drug-Resistant Cancer Cells

Interestingly, HDAC inhibitors exert divergent effects on MDR1 expression in drug-resistant cancer cell lines. For example, TSA, which up-regulated MDR1 mRNA and functional activity in wild-type MCF-7 breast cancer cells, did not affect MDR1 mRNA in drug-resistant MCF-7 cells at comparable concentrations and treatment duration (Toth et al., 2012). In H69 lung cancer cells, the effects of TSA were even in an opposite direction in drug-resistant cells, causing significant reduction of MDR1 mRNA (El-Khoury et al., 2007). Like TSA, sodium butyrate increased MDR1 mRNA in wild-type H69 cells, but decreased its expression in resistant cells (El-Khoury et al., 2007). Also, SAHA down-regulated both the mRNA and protein expression of MDR1 in drug-resistant SK-N-SH and SK-N-Be(2)C neuroblastoma cells while it caused no change in matching wild-type cells (Lautz et al., 2012). Overall, HDAC inhibitors appear to down-regulate MDR1 in resistant cancer cells. Such differential effects may be related to: (1) a higher baseline MDR1 expression and function in the resistant cells compared to the corresponding wild-type; (2) active efflux potentially of some HDAC inhibitors in drug-resistant cells; and (3) an altered gene expression profile of the resistant cells that affects the pharmacological activity of HDAC inhibitors. Also, it is possible that effects of HDAC inhibitors on cell proliferation, which can indirectly affect the MDR1 levels, may vary between sensitive and resistant cancer cells.

5.1.5. Summary and Conclusion

Different classes of HDAC inhibitors are capable of up-regulating the expression and/or activity of the MDR1 transporter although there is selectivity and specificity in the responses. Important factors that likely impart specificity in HDAC inhibitor-mediated regulation of MDR1 include cell types and tissue origins, cellular and molecular environments, chemical's potency for inhibiting HDAC enzymes, the

relative toxicity of the chemicals in different cell types, and the duration of chemical treatment. In general, hydroxamic acids, which are relatively potent pan-HDAC inhibitors targeting a wide range of HDAC isoforms, can alter the MDR1 expression and function in a wide variety of cells though in different manners. Similarly, SCFAs were shown to influence MDR1 in various cell types but the effects of these HDAC inhibitors may be limited due to their weak potency. In contrast, cyclic peptides demonstrated more potent and selective activity, possibly due to the selective HDAC enzyme targets of these compounds. All classes of HDAC inhibitors showed some potential for modulating MDR1 *in vivo* although whether these responses are clinically relevant based on known pharmacokinetic exposures is unknown. Some of the divergent effects of HDAC inhibitors between studies may be simply due to different experimental conditions across laboratories. The relative efficiency and potency of HDAC inhibitors in different systems can be more clearly elucidated by conducting a comprehensive study assessing MDR1 modulation in different representative cell types (for example, cancerous versus non-cancerous cells, sensitive versus resistant cancer cells, and immortalized versus primary cells) treated with HDAC inhibitors over the range of concentrations and treatment durations.

6. EFFECTS OF HDAC INHIBITORS ON THE BCRP TRANSPORTER

Similar to the MDR1 transporter, BCRP can also be up-regulated by HDAC inhibitors although some diverging findings have been observed (**Table 5**). Different classes of HDAC inhibitors are able to induce BCRP mRNA in various human hematological tumor cells including KG1a, HL-60, CMK and K562 leukemia cell lines at similar concentrations and time points that induced MDR1 (Hauswald et al., 2009; Fuchs et al., 2010). In some cell lines, increases in mRNA expression translated into protein up-regulation and enhanced efflux function. Like MDR1, the expression of BCRP in drug-resistant KB cells was resistant to modulation by HDAC inhibitors: neither SAHA nor apicidin were able to alter BCRP transporter expression after 24 h of treatment at increasing concentrations (Kim et al., 2011). In S1 colon carcinoma cells, BCRP mRNA levels, like MDR1, were induced by HDAC inhibitors (To et al., 2008; To et al., 2011). Furthermore, HDAC inhibitors upregulated BCRP protein expression and transport activity in S1 cells (To

et al., 2011). Likewise, BCRP mRNA and protein levels as well as the functional activity were induced by VPA, a SCFA HDAC inhibitor, in a time- and concentration-dependent manner (Rubinchik-Stern et al., 2015). As discussed in the previous section, *ABCB1* and *ABCG2* promoter regions share some common features. Therefore, it is likely that shared molecular mechanisms are utilized by HDAC inhibitors in those cells where MDR1 and BCRP transporters are similarly regulated.

BCRP up-regulation by HDAC inhibitors has been shown to be mediated in a chemical-specific manner in some cells (Basseville et al., 2012). In Flp-In HEK293 cells transfected with the wild-type *ABCG2* gene, SAHA, panobinostat, and romidepsin, which are potent HDAC inhibitors, significantly up-regulated both the mRNA and protein expression of BCRP. This change in the expression was reflected in enhanced function as observed by the reduced cytotoxicity of pheophorbide A, a BCRP substrate, in the presence of HDAC inhibitors. By contrast, VPA, a weak HDAC inhibitor, was not able to alter either the expression or the function of BCRP in the same cell line. Differential regulation of BCRP by different HDAC inhibitors may be related to chemical potency or molecular mechanisms. Higher concentrations of VPA may increase BCRP expression, but could also be accompanied by greater toxicity to the cells.

In certain cases, BCRP expression appeared to change more sensitively than MDR1 in response to HDAC inhibition. For example, in 127 and 143 human renal cell carcinoma cells, romidepsin notably induced BCRP mRNA whereas MDR1 expression was not altered (Robey et al., 2006). Similarly, sodium butyrate and romidepsin at their maximal non-toxic concentrations in hCMEC/D3 brain endothelial cells did not alter MDR1 mRNA levels, but significantly increased BCRP mRNA expression (You et al., 2019b). It is possible that in these cells where no changes in MDR1 were observed, tested HDAC inhibitors may modulate BCRP transporters via distinctive molecular pathways.

Interestingly, HDAC inhibitors caused down-regulation of BCRP in some cell types. For example, in MCF-7 breast cancer cells, cyclic peptide romidepsin decreased the mRNA levels of BCRP while it increased MDR1 mRNA (To et al., 2008). Likewise, hydroxamate HDAC inhibitors SAHA and panobinostat, which induced MDR1 mRNA in SF295 glioblastoma cells, down-regulated BCRP mRNA expression and activity in these cells (To et al., 2011). The effects of romidepsin on BCRP mRNA in SF295

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cells also included repression. Similarly, SAHA as well as TSA, another hydroxamate HDAC inhibitor, significantly elevated MDR1 mRNA and protein expression but reduced BCRP mRNA level in A549 lung cancer cells (Wang et al., 2019). These results suggest that in those cells with diverging responses for BCRP and MDR1 transporters after HDAC inhibitor treatment: (1) the overall transport function is more tightly regulated and thus HDAC inhibitors cause compensatory down-regulation of BCRP transporter in response to the MDR1 induction; or (2) HDAC inhibitors may differentially activate molecular pathways to modulate the two transporters.

In conclusion, more diverse patterns of HDAC inhibitor-mediated regulation have been observed for the BCRP transporter. Data from the studies presented support the contention that BCRP and MDR1 transporters are regulated by HDAC inhibitors through distinct mechanisms. However, because of the functional overlap (similar locations and substrate specificity) between these two transporters, regulation of the BCRP and MDR1 transporters may be interdependent.

7. POTENTIAL MECHANISMS OF HDAC INHIBITOR-MEDIATED TRANSPORTER REGULATION

Several studies have delved deeper to delineate the mechanisms by which HDAC inhibitors alter efflux transporter expression in various cell types. These studies have consistently revealed a correlation between transporter regulation and alterations in the acetylation status of histones in response to HDAC inhibitors (Jin and Scotto, 1998; El-Osta et al., 2002; Baker et al., 2005; Tabe et al., 2006; El-Khoury et al., 2007; Kim et al., 2008; Hauswald et al., 2009; Kim et al., 2009; Valdez et al., 2016; You et al., 2019a; You et al., 2019b). Such association confirmed that HDAC inhibitors did in fact prevent the de-acetylation of histone proteins. Increases in global acetylation of both histone H3 and H4 proteins were observed after exposure to HDAC inhibitors, though to varying extents depending upon the cell type. A study by Kim et. al. (2008) showed that there were dose-dependent increases in acetylated histone proteins that correlated with induction of MDR1 protein (Kim et al., 2008). Also, VPA- and apicidin-mediated up-regulation of Mdr1 and Bcrp protein in different regions of mouse brains was accompanied by increases in acetylated

histone H3 proteins (You et al., 2019a). Valdez and coworkers (2016) showed that the histone acetylation was observed earlier than the induction of MDR1, suggesting that acetylation of histones was a preceding event for MDR1 induction (Valdez et al., 2016). Histone acetylation was observed particularly at the regions nearby the promoter regions of *ABCB1* and *ABCG2* genes after the treatment with HDAC inhibitors (Jin and Scotto, 1998; Baker et al., 2005; Xiao et al., 2005; Tabe et al., 2006; El-Khoury et al., 2007; Hauswald et al., 2009; Kim et al., 2009). Altogether, these data suggested that transporter up-regulation by HDAC inhibitors occurs through increasing the accessibility of transporter gene promoter sequences and consequently promoting gene transcription.

Indeed, the presence of actinomycin D, which is a transcriptional inhibitor, negated the induction of MDR1 by TSA (Baker et al., 2005; El-Khoury et al., 2007). This result confirmed that up-regulation of MDR1 by TSA occurred at the transcriptional level. Jin and Scotto demonstrated that sequences in a DSP region of *ABCB1* gene were critical for TSA-mediated activation of gene transcription (Jin and Scotto, 1998). As discussed previously in this review, the sequence from -134 to +286 bp is critical for effective transcription of the *ABCB1* gene (Cornwell, 1990; Goldsmith et al., 1993; Madden et al., 1993). In their study, Jin and Scotto assessed the relative activation of different stably transfected *ABCB1* promoter deletion constructs by TSA in SW620 cells, and observed that the sequences from -136 to -75 bp, which contain potential binding sites for critical transcription factors, were important for TSA-mediated activation of MDR1 (Jin and Scotto, 1998). Particularly, an inverted CCAAT box element (Y box, -82 to -73 bp) was found to be the most important region to mediate TSA activity: mutations specifically in the Y box region significantly reduced *ABCB1* promoter activation by TSA (Jin and Scotto, 1998). Likewise, MDR1 induction by SAHA in immortalized brain endothelial hCMEC/D3 cells involved the most significant increases in histone H3 acetylation at the region from -100 to +8 bp which contains the Y box, GC box, as well as a putative DRE, a binding site for AHR (You et al., 2019b).

ABCB1 gene activation by other classes of HDAC inhibitors also involved sequences at the DSP region. In their study, Jin and Scotto (1998) showed that sodium butyrate, a SCFA HDAC inhibitor, activated the *ABCB1* promoter in SW620 cells through a Y box (Jin and Scotto, 1998). Likewise, the cyclic

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peptide HDAC inhibitor, apicidin, mediated induction of MDR1 through transactivation of the Y box region. The study by Kim and his colleagues (2009) revealed that apicidin increased histone H3 acetylation in HeLa cells at the *ABCB1* promoter region from -160 to +85 bp which contains numerous transcription factor binding sites including Y box, GC boxes, and a DRE (Kim et al., 2009). Moreover, mutation of the Y box region negated the ability of apicidin to activate *ABCB1* promoter luciferase constructs transfected into HeLa cells (Kim et al., 2009). Altogether, these results suggest that the sequences at the DSP region of the *ABCB1* gene are commonly required by different HDAC inhibitors in order to induce MDR1.

Yet, the specific transcription factors that are involved in *ABCB1* gene activation appear to differ across various HDAC inhibitors. Jin and Scotto showed that the binding of NF-Y at Y box was important to mediate the activity of TSA in SW620 cells (Jin and Scotto, 1998). The authors further observed that the activity of P300/CBP-associated factor (PCAF), a HAT-containing transcriptional co-activator, also depended upon a Y box. In an *in vitro* transcription-translation and pull-down assay, NF-Y alpha subunit (NF-YA) and PCAF were shown to interact. From these results, the authors concluded that inhibition of HDACs by TSA increases the activity of PCAF which is recruited to the Y box through its interaction with NF-YA. This would consequently result in an increased histone acetylation and a perturbed nucleosome structure around the *ABCB1* promoter, leading to *ABCB1* transcriptional activation (Jin and Scotto, 1998). The importance of PCAF activity in TSA-mediated MDR1 activation was also investigated in the study by El-Khoury and coworkers (2007). They observed MDR1 mRNA induction as well as increased PCAF binding to the Y box of *ABCB1* promoter in wild-type H69 lung carcinoma cells treated with TSA. Interestingly, PCAF occupancy at the *ABCB1* promoter was also increased, though to a lesser extent, in resistant H69 cells where TSA caused reduction of MDR1 mRNA (El-Khoury et al., 2007). This suggests that factors other than PCAF play a major role in the suppression of MDR1 gene transcription in H69 resistant cells.

By contrast, AHR seemed to play a critical role in MDR1 up-regulation by SAHA, another hydroxamate HDAC inhibitor, in hCMEC/D3 cells (You et al., 2019b). Our recent study showed that SAHA significantly increased the histone H3 acetylation as well as AHR binding at *ABCB1* DSP region (-100 to

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+8 bp) where a putative DRE for AHR, a regulator of MDR1, is located, suggesting that histone acetylation mediated by SAHA and subsequent AHR binding at *ABCB1* promoter activates *ABCB1* gene transcription. Moreover, SAHA-mediated increases in MDR1 mRNA and protein levels in hCMEC/D3 were further enhanced in the presence of an AHR activator, but significantly reduced in the presence of an AHR inhibitor. Yet, SAHA's ability to up-regulate MDR1 activity was not completely reversed by AHR inhibition. Since SAHA has a wide range of molecular targets, it is likely that SAHA modulates additional pathways that can also contribute to MDR1 induction.

Apicidin-mediated induction of MDR1 was shown to involve the transcription factor, Sp1. In their study, Kim and coworkers observed that co-exposure of HeLa cells to mithramycin, a pharmacologic inhibitor of Sp1 binding to the promoters, could negate the MDR1 induction by apicidin, suggesting the absolute requirement of Sp1 for the action of apicidin (Kim et al., 2009). Interestingly, this study observed that apicidin did not change the amount of Sp1 binding at *ABCB1* promoter while it did cause HDAC1 dissociation from and recruit transcription factors PCAF, C/EBPβ, and Pol II to the *ABCB1* promoter. Instead, apicidin significantly increased Sp1 phosphorylation, which is critical for the activity of this transcription factor. Further analyses showed that the presence of LY294002, an inhibitor of phosphatidylinositol 3-kinase (PI3K) signaling pathway, strongly inhibited Sp1 phosphorylation, transcription machinery binding to *ABCB1* promoter, and MDR1 up-regulation after apicidin exposure (Kim et al., 2009). From these observations, the authors concluded that apicidin causes PI3K-mediated phosphorylation of Sp1 which then facilitates HDAC1 dissociation and subsequently binding of transcription factors to activate transcription. Collectively, these results imply that HDAC inhibitors can trigger unique molecular events around the *ABCB1* promoter to cause mRNA transcription across different cell lines. This may explain chemical-specific or cell type-specific changes in MDR1 regulation observed with different classes of HDAC inhibitors.

Promoter methylation has emerged as an important factor in the interaction between histone acetylation and transcription of the *ABCB1* gene. Previous studies observed that TSA alone could not induce MDR1 mRNA in CEM-CCRF acute lymphoblastic leukemia cells which have a hypermethylated *ABCB1*

promoter (El-Osta et al., 2002; Baker et al., 2005). However, co-treatment with TSA and 5-azacytidine (5aC), a DNA methyltransferase inhibitor, caused a robust increase in MDR1 mRNA in CEM-CCRF cells (El-Osta et al., 2002; Baker et al., 2005). In contrast, MDR1 mRNA expression in CEM-A7R and CEM-Bcl2 cells, which have hypomethylated *ABCB1* promoters, was significantly up-regulated by TSA, and this induction was not further elevated by the addition of 5aC (El-Osta et al., 2002; Baker et al., 2005). From these results, the authors concluded that CpG methylation at the *ABCB1* promoter is a critical silencer of *ABCB1* transcription and that histone acetylation alone is not sufficient to activate hypermethylated *ABCB1* gene. However, the difference in CpG methylation status does not appear to be the only determinant of the variable effects of TSA on MDR1. In their study, El-Khoury and coworkers (2007) found that wild-type and drug-resistant H69 lung carcinoma cells, both of which showed hypomethylation at *MDR1* promoter, responded differently to TSA. TSA induced MDR1 mRNA in wild-type cells, but decreased its expression in resistant cells (El-Khoury et al., 2007). Collectively, these results imply that there is no single dominant factor but rather multiple interacting factors that regulate the mechanisms by which HDAC inhibitors alter MDR1 expression.

Induction of BCRP expression in the plasma membrane by various HDAC inhibitors including romidepsin, SAHA, and VPA was also abrogated in the presence of actinomycin D, implying that HDAC inhibitor-mediated induction of BCRP is also mediated at the transcriptional level (Basseville et al., 2012). Investigation of the molecular mechanisms underlying BCRP induction by HDAC inhibitors revealed increased histone H3 acetylation at the proximal region of the *ABCG2* promoter (-687 to +20 bp) in S1 colon cancer cells treated with romidepsin, with the most consistent change seen at the sequence from -293 to -193 bp (position “P3”) (To et al., 2008). Romidepsin also decreased the binding of HDAC1 and 3 at “P3.” Investigation of the molecular events occurring at “P3” in S1 cells revealed increased binding of AHR, a known BCRP-regulating transcription factor, at that site. Genetic knockdown of AHR reversed the BCRP induction by romidepsin, confirming that the activity of AHR was critical for BCRP regulation by romidepsin, as it was for MDR1 regulation by SAHA (To et al., 2011; You et al., 2019b).

Further analysis showed that romidepsin acetylated Hsp70 to disrupt the chaperone function of Hsp90. Acetylation of Hsp70 indirectly facilitates the dissociation between AHR and Hsp90, thereby increasing AHR activity and consequently activating the *ABCG2* gene by AHR (To et al., 2011). The authors also observed that SAHA caused similar induction of BCRP mRNA and function as well as acetylation of Hsp70 in S1 cells, suggesting that AHR may also play a critical role in SAHA-mediated induction of BCRP in this cell line. Interestingly, SAHA also acetylated Hsp90 unlike romidepsin which caused acetylation only on Hsp70, implying that SAHA causes more non-specific acetylation of proteins in these cells. Therefore, these results further support the contention that SAHA targets multiple molecular pathways that can together influence transporter up-regulation (To et al., 2011; You et al., 2019b). In SW620 cells, romidepsin caused neither AHR binding at the *ABCG2* promoter nor acetylation of Hsp70 or Hsp90, which likely accounts for the unresponsiveness of SW620 cells to romidepsin-mediated regulation of BCRP (To et al., 2011). These results further illustrate the highly specific effects of HDAC inhibitor on regulating transporter expression across cell types.

Because HDAC inhibitors have several different molecular activities, it is possible that these compounds indirectly regulate MDR1 and BCRP by impacting the expression and/or activity of the transcriptional regulators of these transporters. Increases in global histone acetylation by HDAC inhibitors may likely affect the transcription of genes other than transporters. Indeed, Garrison and the colleagues demonstrated that TSA and butyrate can increase the promoter activity of *Ahr*, a known transcriptional regulator of MDR1 and BCRP (Garrison et al., 2000). In addition, some HDAC inhibitors are thought to activate the xenobiotic-activated transcription factors that regulate MDR1 and BCRP. VPA was shown to activate constitutive androstane receptor (CAR) and consequently induce the transcription of MDR1 in human liver cancer HepG2 cells (Cerveny et al., 2007). Such ability to activate CAR was also demonstrated for other HDAC inhibitors, though to different extents (Takizawa et al., 2010). As suggested earlier in this section, HDAC inhibitors may exert their regulatory activites on MDR1 and BCRP through multiple mechanisms, which can include both direct interaction with the transporter genes and indirect modulation

as discussed here. The ability for this indirect regulation of the transporters may also contribute to the chemical-specific and cell-type changes in the transporters by HDAC inhibitors.

HDAC inhibitors targets multiple isoforms of HDACs and can elicit effects beyond transporter regulation. Therefore, studies have performed genetic knockdown of HDACs and identified specific HDAC isoforms responsible for transporters (**Table 6**). Studies have largely focused on class I HDACs, which are nuclear HDACs that possess an intrinsic capability to deacetylate core histones (Hassig et al., 1998; Hu et al., 2000; Johnson et al., 2002). As observed with HDAC inhibitors, the effects of HDAC knockdown were also highly variable between across cell lines. For example, HDAC1 siRNA effectively increased MDR1 mRNA and protein in wild-type HCT-8 and HCT-116 colon carcinoma cells, while it did not affect MDR1 expression in BeWo or JAR trophoblast cells (Xu et al., 2012; Duan et al., 2017b). HDAC2 siRNA knockdown resulted in the differential regulation of MDR1 between different colon carcinoma cells. Reduction in HDAC2 protein expression leads to up-regulated MDR1 expression in HCT-8 cells whereas a decrease in MDR1 level was observed in SW480 colon cancer cells transfected with HDAC2 siRNA (Xu et al., 2012; Ye et al., 2016). Unlike HDAC1 knockdown, genetic silencing of HDAC2 significantly increased both the expression and function of MDR1 in BeWo and JAR cells (Duan et al., 2017b). Furthermore, the up-regulation of Abcb1a mRNA and Mdr1 protein levels were observed in the placentas of pregnant dams injected with Hdac2 siRNA from embryonic day 7.5 to 15.5 (Duan et al., 2017b). HDAC3 knockdown up-regulated the protein expression of MDR1 as well as acetylated histone H3K9/14 and H4K16 in Malme3M melanoma cells and SNU387 hepatocellular carcinoma cells (Park et al., 2014). However, knocking down HDAC3 caused no change in MDR1 expression or function in BeWo or JAR cells (Duan et al., 2017b). Factors such as the relative expression of HDACs or their associated proteins in different cell types may play roles in differentially regulating transporters following knockdown of specific HDAC isoforms.

8. CONCLUSION AND DISCUSSION

MDR1 and BCRP control the passage of diverse chemicals in several key organs such as the liver, kidneys, and brain. They also regulate the responsiveness of cancer cells to chemotherapeutic drugs. A comprehensive understanding of how these transporters can be regulated is important in identifying factors controlling the efficacy and toxicity of chemicals. The evidence reviewed in this paper strongly suggest that the expression of the MDR1 and BCRP transporters can be modulated by histone acetylation following inhibition of HDAC enzymes. Various factors such as differences in biological properties and molecular environments across different cell types, the characteristics of HDAC inhibitors including specificity and potency, and disease conditions seem to interact and determine the ability of HDAC inhibition to regulate these efflux transporters. Also, the molecular events induced by different HDAC inhibitors in various cells can be highly specific and the regulation of efflux transporters by these compounds can be quite complex. Other important factors such as differences in species and gender, which are not yet fully investigated, are also likely to affect transporter regulation by HDAC inhibitors. Further studies comprehensively assessing the molecular targets of each HDAC inhibitor as well as the transcription factors interacting with *ABCB1* and *ABCG2* genes upon HDAC inhibition will provide a more complete understanding of the differential regulation of MDR1 and BCRP transporters by these epigenetic modulators. A more complete understanding will also allow us to better predict how HDAC inhibitors will affect efflux transporter expression in different individuals with varying genetic background, age, pre-existing disease conditions, and co-administered drugs. Importantly, more investigations should be performed to assess the effects of HDAC inhibitors on the transporter activity in non-cancerous organs, particularly liver, kidney, and intestine which play key roles in drug disposition. Ultimately, we should recognize and assess the clinical conseqences of using HDAC inhibitors where the activity of efflux transporters plays a key role in determining tissue exposure to drugs and toxicants. Such studies will help us identify potential drug interactions caused by HDAC inhibitors, which are often co-administered with other drugs that are substrates of MDR1 and BCRP transporters.

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FOOTNOTES

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FIGURE LEGENDS

Figure 1. Regulatory Elements at the Human *ABCB1* Gene Promoter. The location of key transcription factor binding sites in the human *ABCB1* promoter are shown as the number of base pairs relative to the transcriptional start site (TSS).

Figure 2. Regulatory Elements at the Human *ABCG2* Gene Promoter. The location of key transcription factor binding sites in the human *ABCG2* promoter are shown as the number of base pairs relative to the transcriptional start site (TSS).

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Table 1. Example Substrates and Inhibitors for the MDR1 and BCRP Transporters

MDR1 Substrates	BCRP Substrates
Doxorubicin, vinblastine, tyrosine kinase inhibitors, HIV protease inhibitors (ritonavir, indinavir), phenytoin, prazosin, digoxin, diltiazem, tetracycline, morphine, polycyclic compounds (steroid aldosterone), fluorescent dyes (Rhodamine 123), amyloid- β, phospholipids and lipid-derived signaling molecules	Doxorubicin, methotrexate, tyrosine kinase inhibitors, mitoxantrone, antiviral drugs (abacavir, zidovudine), fluoroquinolone antibiotics, prazosin, glyburide, etoposide, topotecan, zearalenone, aflatoxin B, fluorescent dyes (Hoechst 33342, Rhodamine 123), Genistein, protoporphyrin IX, amyloid-β, cholate
MDR1 Inhibitors	**BCRP Inhibitors**
Verapamil, cyclic peptides (cyclosporin A, PSC833), tamoxifen, sildanefil, curcuminoids, flavonoids, LY335979 (zosuquidar), GF120918 (elacridar)	Ko143, omeprazole, fumitremorgin C, GF120918 (elacridar), tyrosine kinase inhibitors, tacrolimus, tamoxifen, cyclosporin A

Table 2. Classes of HDACs and their Subcellular Localizations

Family	Class	Members	Primary Location
Classical, Zinc-Dependent (HDACs)	I	1, 2	Nucleus
		3, 8	Nucleus & Cytoplasm
	IIa	4, 5, 7, 9	Nucleus & Cytoplasm
	IIb	6	Cytoplasm
		10	Nucleus & Cytoplasm
	IV	11	Nucleus & Cytoplasm
Sirtuins, NAD-Dependent (SIRTs)	III	1, 2	Nucleus & Cytoplasm
		3	Nucleus & Mitochondria
		4, 5	Mitochondria
		6	Nucleus
		7	Nucleolus

Table 3. Classes of HDAC Inhibitors and Their Targets

Class	Examples	HDAC Targets	Potency Range[1]
Hydroxamates	SAHA, Trichostatin A (TSA), Belinostat, Panobinostat	Class I and IIb	nM – μM
Short Chain Fatty Acids	Valproic Acid (VPA), Sodium Butyrate, Phenylbutyrate	Class I and IIa	mM
Cyclic Peptides	Romidepsin, Apicidin	Class I	nM
Benzamides	MS-275, Mocetinostat, CI-994	Class I	μM

[1]This potency range represents general IC_{50} values (50% inhibitory concentrations) for purified HDACs as determined by HDAC activity assays.

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Table 4. Effects of HDAC Inhibitors on the Regulation of MDR1 Across Various Cell Types

Human Cells					
Organ	**Cells**	**HDACi Class**	**Agent**	**Observation**	**References**
Blood	CEM-Bcl2	HA	TSA	↑[m] ↔[p]	(Baker et al., 2005)
	CEM-CCRF	HA	TSA	↔[m]	(El-Osta et al., 2002)
	CEM-A7R (R)	HA	TSA	↑[m]	(El-Osta et al., 2002)
	KG1a	HA	TSA	↑[m]	(Eyal et al., 2006; Hauswald et al., 2009; Fuchs et al., 2010)
			SAHA	↑[m]	
		SCFA	VPA	↑[m] ↑[a]	
			Butyrate	↑[m] ↑[p] ↑[a]	
	HL-60	HA	TSA	↑[m]	(Hauswald et al., 2009)
			SAHA	↑[m]	
		SCFA	VPA	↑[m]	
			Butyrate	↑[m]	
	CMK	HA	TSA	↑[m]	(Hauswald et al., 2009)
		SCFA	VPA	↑[m] ↑[a]	
			Butyrate	↑[m] ↑[p] ↑[a]	
	K562	HA	TSA	↑[m] ↔[a]	(Xiao et al., 2005; Hauswald et al., 2009; Balaguer et al., 2012)
			SAHA	↑[m]	
		SCFA	VPA	↑[m]	
			Butyrate	↑[m]	
		CP	Romidepsin	↑[m]	
	K562 (R)	HA	TSA	↓[m] ↑[a]	(Balaguer et al., 2012)
	PEER	HA	SAHA	↑[p]	(Valdez et al., 2016)
			Panobinostat	↑[m] ↑[p] ↑[a]	
			Belinostat	↓[p]	
		CP	Romidepsin	↑[m] ↑[p] ↑[a]	
		BZ	LMK-235	↔[p]	
	MV4-11	HA	Panobinostat	↔[p]	(Valdez et al., 2016)
		CP	Romidepsin	↔[p]	
	CMK	SCFA	VPA	↑[m] ↑[a]	(Hauswald et al., 2009)
	DAUDI	HA	Panobinostat	↑[p]	(Valdez et al., 2016)
		CP	Romidepsin	↑[p]	

HDACi: HDAC inhibitor; HA: Hydroxamic acid; SCFA: Short chain fatty acids; CP: Cyclic peptides; BZ: Benzamides; TSA: Trichostatin A; SAHA: Suberoylanilide hydroxamic acid; VPA: Valproic acid; m: mRNA; p: Protein; a: Activity

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Table 4. Effects of HDAC Inhibitors on the Regulation of MDR1 Across Various Cell Types (Cont.)

Human Cells					
Organ	**Cells**	**HDACi Class**	**Agent**	**Observation**	**References**
Blood	NB4	CP	Romidepsin	↑[m]	(Tabe et al., 2006)
	Leukemia Primary mononuclear cells	HA	SAHA	↑[m] ↔[p] ↔[a]	(Odenike et al., 2008; Hauswald et al., 2009; Gojo et al., 2013; Odenike et al., 2015)
			Belinostat	↑[m]	
		SCFA	VPA	↑[m]	
			Butyrate	↑[m] ↑[a]	
		CP	Romidepsin	↑[m]	
	Lymphoma Primary mononuclear Cells	CP	Romidepsin	↔/↑[m] ↑[p]	(Robey et al., 2006; Bates et al., 2010; Valdez et al., 2016)
Brain	SF295	HA	SAHA	↑[m]	(To et al., 2008; To et al., 2011)
			Panobinostat	↑[m]	
		CP	Romidepsin	↑[m]	
	A172 & U87	CP	Apicidin	↔[m]	(Kim et al., 2009)
	hCMEC/D3	HA	TSA	↑[m] ↑[p]	(You et al., 2019b)
			SAHA	↑[m] ↑[p] ↑[a]	
		SCFA	VPA	↑[m] ↑[p] ↑[a]	
			Butyrate	↔[m] ↔[p]	
		CP	Apicidin	↑[m] ↑[p] ↑[a]	
			Romidepsin	↔[m] ↔[p]	
Breast	MCF-7	HA	TSA	↑[m] ↑[a]	(Xiao et al., 2005; To et al., 2008; Balaguer et al., 2012; Toth et al., 2012)
		CP	Romidepsin	↑[m]	
	MCF-7 (R)	HA	TSA	↔/↓[m]	(Balaguer et al., 2012; Toth et al., 2012)
Cervix	HeLa	HA	TSA	↑[m] ↑[p]	(Kim et al., 2008; Kim et al., 2009; Huo et al., 2010)
			SAHA	↑[m]	
		SCFA	VPA	↑[m]	
			Butyrate	↑[m]	
		CP	Apicidin	↑[m] ↑[p] ↑[a]	
		BZ	MS-275	↑[m]	
	SiHa	CP	Apicidin	↑[m]	(Kim et al., 2009)

HDACi: HDAC inhibitor; HA: Hydroxamic acid; SCFA: Short chain fatty acids; CP: Cyclic peptides; BZ: Benzamides; TSA: Trichostatin A; SAHA: Suberoylanilide hydroxamic acid; VPA: Valproic acid; m: mRNA; p: Protein; a: Activity

[1]The authors misidentified these cell lines in their study as oral cancer cells.

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Table 4. Effects of HDAC Inhibitors on the Regulation of MDR1 Across Various Cell Types (Cont.)

Human Cells					
Organ	**Cells**	**HDACi Class**	**Agent**	**Observation**	**References**
Cervix	KB[1]	HA	TSA	↔[m]	(Kim et al., 2008; Kim et al., 2009)
			SAHA	↔[m]	
		SCFA	VPA	↔[m]	
			Butyrate	↔[m]	
		CP	Apicidin	↔[m]	
		BZ	MS-275	↔[m]	
	KB (R)[1]	HA	TSA	↔[m]	(Kim et al., 2011)
			SAHA	↔[m]	
		CP	Apicidin	↔[m]	
		BZ	MS-275	↔[m]	
Colon	SW620	HA	TSA	↑[m] ↑[p] ↔[a]	(Bates et al., 1992; Frommel et al., 1993; Morrow et al., 1994; Jin and Scotto, 1998; Baker et al., 2005; Eyal et al., 2006; Robey et al., 2006; Gomez-Martinez et al., 2007; To et al., 2008; To et al., 2011; Pasvanis et al., 2012)
			SAHA	↑[m]	
			Panobinostat	↑[m]	
		SCFA	VPA	↑[p]	
			Butyrate	↑[m] ↑[p] ↑[a]	
		CP	Romidepsin	↑[m] ↑[p] ↑[a]	
	LoVo	HA	TSA	↔[m]	(Lee et al., 2008)
	Colo320HSR	HA	TSA	↑[m]	(Lee et al., 2008)
	HCT-116	HA	TSA	↑[m] ↑[p]	(Lee et al., 2008; Xu et al., 2012; Wang et al., 2019)
			SAHA	↑[m] ↑[p]	
	HCT-8	HA	TSA	↔[m]	(Lee et al., 2008; Xu et al., 2012)
			SAHA	↑[m] ↑[p]	
	HCT-15	SCFA	Butyrate	↑[m] ↑[p] ↑[a]	(Frommel et al., 1993)
	DLD-1	HA	TSA	↑[m]	(Lee et al., 2008; Kim et al., 2009)
		CP	Apicidin	↑[m]	
		SCFA	Butyrate	↑[m] ↑[p] ↑[a]	(Frommel et al., 1993)
	S1	HA	SAHA	↑[m]	(To et al., 2008; To et al., 2011)
			Panobinostat	↑[m]	
		CP	Romidepsin	↑[m]	

HDACi: HDAC inhibitor; HA: Hydroxamic acid; SCFA: Short chain fatty acids; CP: Cyclic peptides; BZ: Benzamides; TSA: Trichostatin A; SAHA: Suberoylanilide hydroxamic acid; VPA: Valproic acid; m: mRNA; p: Protein; a: Activity

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Human Cells					
Organ	**Cells**	**HDACi Class**	**Agent**	**Observation**	**References**
Colon	SNU-C1	HA	TSA	↑[m]	(Lee et al., 2008)
	SNU-C4	HA	TSA	↔[m]	(Lee et al., 2008)
	Caco-2	SCFA	Butyrate	↑[m] ↑[p] ↑[a]	(Pasvanis et al., 2012; Yan et al., 2017)
	HT-29	HA	TSA	↑[m] ↔[p] ↔[a]	(Gomez-Martinez et al., 2007)
	HT-29 (R)	HA	TSA	↑[m] ↔[p] ↔[a]	(Gomez-Martinez et al., 2007)
Kidney	108, 121	CP	Romidepsin	↑[m] ↑[a]	(Robey et al., 2006)
	127, 143	CP	Romidepsin	↔[m]	(Robey et al., 2006)
Liver	SK-Hep-1	HA	SAHA	↑[m]	(Hauswald et al., 2009)
	HepG2	SCFA	VPA	↑[m]	(Cerveny et al., 2007)
Lung	H69	HA	TSA	↑[m]	(El-Khoury et al., 2007)
		SCFA	Butyrate	↑[m]	
	H69 (R)	HA	TSA	↓[m]	(El-Khoury et al., 2007)
		SCFA	Butyrate	↓[m]	
	A549	HA	TSA	↑[m] ↔/↑[p]	(Kaewpiboon et al., 2015; Wang et al., 2019)
			SAHA	↑[m] ↑[p]	(Wang et al., 2019)
		SCFA	Butyrate	↑[m] ↑[p]	(Zhao et al., 2018)
	A549 (R)	HA	TSA	↓[m] ↓[p]	(Kaewpiboon et al., 2015)
	H460	CP	Romidepsin	↑[m]	(To et al., 2008)
	H1299	SCFA	Butyrate	↑[m] ↑[p]	(Zhao et al., 2018)
	SK-mes-1	SCFA	Butyrate	↑[m] ↑[p]	(Zhao et al., 2018)
Nerves	SK-N-SH cells	HA	SAHA	↔[p]	(Lautz et al., 2012)
	SK-N-Sh cells (R)	HA	SAHA	↓[m] ↓[p]	(Lautz et al., 2012)
	SK-N-Be(2)C cells	HA	SAHA	↔[p]	(Lautz et al., 2012)
	SK-N-Be(2)C cells (R)	HA	SAHA	↓[m] ↓[p]	(Lautz et al., 2012)
Ovary	IGROV1	HA	TSA	↑[m]	(Xiao et al., 2005; Yatouji et al., 2007)
		CP	Romidepsin	↑[m]	
	OC3/P (R)	HA	SAHA	↓[m]	(Liu et al., 2014)
Pancreas	IMIM-PC-1	HA	TSA	↑[m] ↔[p] ↔[a]	(Balaguer et al., 2012)
			SAHA	↑[m]	

HDACi: HDAC inhibitor; HA: Hydroxamic acid; SCFA: Short chain fatty acids; CP: Cyclic peptides; BZ: Benzamides; TSA: Trichostatin A; SAHA: Suberoylanilide hydroxamic acid; VPA: Valproic acid; m: mRNA; p: Protein; a: Activity

Table 4. Effects of HDAC Inhibitors on the Regulation of MDR1 Across Various Cell Types (Cont.)

Human Cells					
Organ	**Cells**	**HDACi Class**	**Agent**	**Observation**	**References**
Pancreas	IMIM-PC-2	HA	TSA	↑[m] ↔[p] ↔[a]	(Balaguer et al., 2012)
			SAHA	↑[m]	
	RWP-1	HA	TSA	↑[m] ↔[p] ↔[a]	(Balaguer et al., 2012)
			SAHA	↑[m]	
	HS766T	HA	TSA	↑[m]	(Balaguer et al., 2012)
	PANC-1	HA	TSA	↑[m]	(Balaguer et al., 2012)
Placenta	BeWo Choriocarcinoma	HA	TSA	↑[m] ↑[p]	(Duan et al., 2017a)
		HA	SAHA	↑[m] ↑[p]	
	JAR Choriocarcinoma	HA	TSA	↑[m] ↑[p]	(Duan et al., 2017a)
		HA	SAHA	↑[m] ↑[p]	
Prostate	LnCap	HA	TSA	↑[m] ↑[p]	(Henrique et al., 2013)
	PC-3	HA	TSA	↑[m] ↑[p]	(Henrique et al., 2013)
	DU143	HA	TSA	↑[m] ↑[p]	(Henrique et al., 2013)
	22RV1	HA	TSA	↑[m]	(Henrique et al., 2013)
Stomach	SNU-1, 16, 216, 601, 638, 668, 719	HA	TSA	↑[m]	(Lee et al., 2008)
	SNU-5	HA	TSA	↔[m]	(Lee et al., 2008)
	SNU-484	HA	TSA	↓[m]	(Lee et al., 2008)
Thyroid	8505C	SCFA	Butyrate	↑[m]	(Massart et al., 2005)
	FTC 238	SCFA	Butyrate	↑[m]	(Massart et al., 2005)
Animal Cells					
Species	**Tissue/Cells**	**HDACi Class**	**Agent**	**Observation**	**References**
Dog	Leukemia GL-1 cells	HA	TSA	↑[m]	(Tomiyasu et al., 2014)
	Lymphoma CLBL-1 cells	HA	TSA	↑[m]	(Tomiyasu et al., 2014)
Rat	Hepatoma D12 cells	HA	TSA	Mdr1a ↓[m] Mdr1b ↑[m]	(Sike et al., 2014)
	Hepatoma D12 cells (R)	HA	TSA	Mdr1a ↓[m] Mdr1b ↑[m]	(Sike et al., 2014)
	Hepatoma H4IIE cells	SCFA	VPA	Mdr1a ↑[m] Mdr1b ↑[m]	(Eyal et al., 2006)

HDACi: HDAC inhibitor; HA: Hydroxamic acid; SCFA: Short chain fatty acids; CP: Cyclic peptides; BZ: Benzamides; TSA: Trichostatin A; SAHA: Suberoylanilide hydroxamic acid; VPA: Valproic acid; m: mRNA; p: Protein; a: Activity

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Table 5. Effects of HDAC Inhibitors on the Regulation of BCRP Across Various Cell Types

Human Cells					
Organ	**Cells**	**HDACi Class**	**Agent**	**Observation**	**References**
Blood	KG1a	HA	TSA	↑[m]	(Hauswald et al., 2009; Fuchs et al., 2010)
			SAHA	↑[m]	
		SCFA	VPA	↑[m] ↑[a]	
			Butyrate	↑[m] ↑[p] ↑[a]	
	HL-60	HA	TSA	↑[m]	(Hauswald et al., 2009)
			SAHA	↑[m]	
		SCFA	VPA	↑[m]	
			Butyrate	↑[m]	
	CMK	HA	TSA	↑[m]	(Hauswald et al., 2009)
			SAHA	↑[m]	
		SCFA	VPA	↑[m] ↑[a]	
			Butyrate	↑[m] ↑[p] ↑[a]	
	K562	HA	TSA	↑[m]	(Hauswald et al., 2009)
		SCFA	VPA	↑[m]	
			Butyrate	↑[m]	
	Leukemia Primary Mononulcear Cells	HA	SAHA	↔/↑[m] ↔[p] ↔[a]	(Hauswald et al., 2009; Kim et al., 2011; Gojo et al., 2013)
		SCFA	VPA	↑[m]	
			Butyrate	↑[m]	
Brain	SF295	HA	SAHA	↓[m] ↓[a]	(To et al., 2008; To et al., 2011)
			Panobinostat	↓[m]	
		CP	Romidepsin	↓[m]	
	hCMEC/D3	HA	TSA	↑[m]	(You et al., 2019b)
			SAHA	↑[m]	
		SCFA	VPA	↑[m]	
			Butyrate	↑[m]	
		CP	Apicidin	↑[m]	
			Romidepsin	↑[m]	
Breast	MCF-7	CP	Romidepsin	↓[m]	(To et al., 2008)
	MCF-7 (R)	HA	Entinostat	↔[m]	(Schech et al., 2015)

HDACi: HDAC inhibitor; HA: Hydroxamic acid; SCFA: Short chain fatty acids; CP: Cyclic peptides; BZ: Benzamides; TSA: Trichostatin A; SAHA: Suberoylanilide hydroxamic acid; VPA: Valproic acid; m: mRNA; p: Protein; a: Activity

[1]The authors misidentified these cell lines in their study as oral cancer cells.

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Table 5. Effects of HDAC Inhibitors on the Regulation of BCRP Across Various Cell Types (Cont.)

Human Cells					
Organ	**Cells**	**HDACi Class**	**Agent**	**Observation**	**References**
Cervix	KB (R)[1]	HA	TSA	↔[m]	(Kim et al., 2011)
			SAHA	↔[m]	
		CP	Apicidin	↔[m]	
		BZ	MS-275	↔[m]	
Colon	SW620	HA	SAHA	↔[a]	(To et al., 2008; To et al., 2011)
	S1	HA	SAHA	↑[m] ↑[a]	(To et al., 2008; To et al., 2011)
			Panobinostat	↑[m]	
		CP	Romidepsin	↑[m] ↑[p] ↑[a]	
	HCT-116	HA	TSA	↔[m] ↔[p]	(Wang et al., 2019)
			SAHA	↔[m] ↔[p]	
Head and neck	KUMA-1	HA	TSA	↓[m] ↓[p]	(Chikamatsu et al., 2013)
			SAHA	↓[m] ↓[p]	
Kidney	108, 121	CP	Romidepsin	↑[m] ↑[a]	(To et al., 2011)
	127, 143	CP	Romidepsin	↑[m]	(To et al., 2011)
Lung	A549	HA	TSA	↓[m] ↔[p]	(Wang et al., 2019)
			SAHA	↓[m] ↔[p]	
	A549 (R)	HA	TSA	↔[m]	(Kaewpiboon et al., 2015)
	H460	CP	Romidepsin	↑[m]	(To et al., 2008)
Placenta	BeWo Choriocarcinoma	SCFA	VPA	↑[m] ↑[p] ↑[a]	(Rubinchik-Stern et al., 2015)

HDACi: HDAC inhibitor; HA: Hydroxamic acid; SCFA: Short chain fatty acids; CP: Cyclic peptides; BZ: Benzamides; TSA: Trichostatin A; SAHA: Suberoylanilide hydroxamic acid; VPA: Valproic acid; m: mRNA; p: Protein; a: Activity

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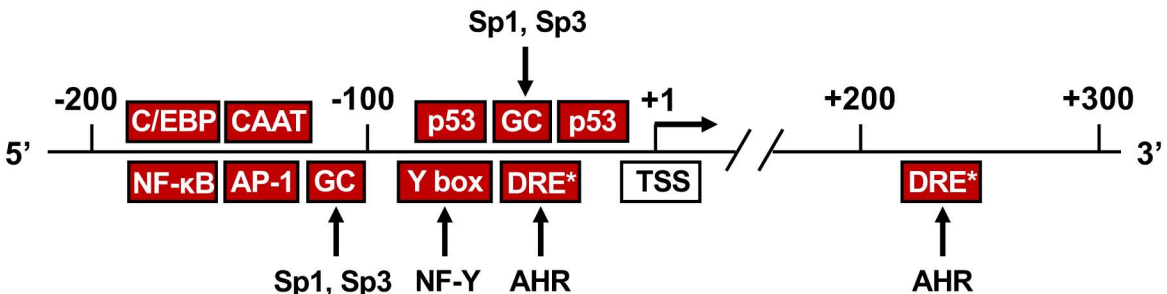
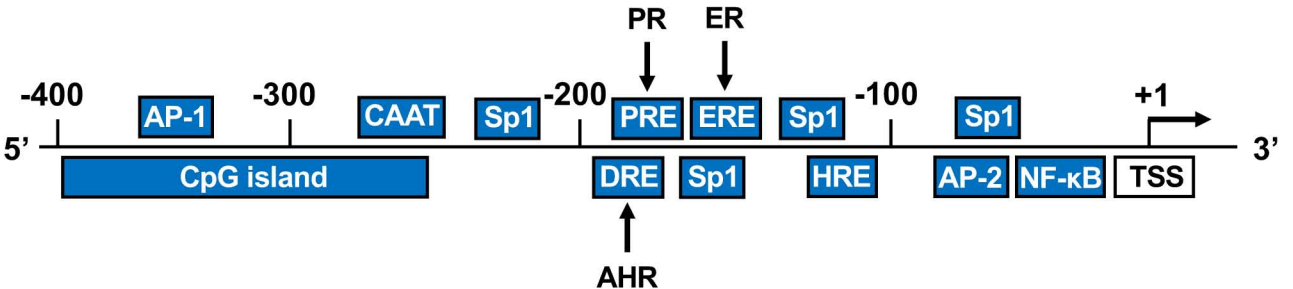
Table 6. Effects of Genetic Modifications of HDACs in Regulating MDR1 and BCRP in Cancer Cells

Gene	Knockdown System	Tissues/Cells	Observation	References
HDAC1	siRNA	Colorectal adenocarcinoma HCT-8 cells	MDR1 ↑[m] ↑[p]	(Xu et al., 2012)
		Colorectal adenocarcinoma HCT-8 cells (R)	MDR1 ↓[m] ↓[p]	(Xu et al., 2012)
		Colorectal carcinoma HCT-116 cells	MDR1 ↑[m] ↑[p]	(Xu et al., 2012)
		Colorectal carcinoma HCT-116 cells (R)	MDR1 ↓[m] ↓[p]	(Xu et al., 2012)
		Cervical adenocarcinoma HeLa cells	MDR1 ↑[m] ↑[p]	(Kim et al., 2009)
		Placental choriocarcinoma BeWo cells	MDR1 ↔[m] ↔[p] ↔[a]	(Duan et al., 2017b)
		Placental choriocarcinoma JAR cells	MDR1 ↔[m] ↔[p] ↔[a]	(Duan et al., 2017b)
HDAC2	siRNA	Colorectal adenocarcinoma HCT-8 cells	MDR1 ↑[m] ↑[p]	(Xu et al., 2012)
		Colorectal adenocarcinoma HCT-8 cells (R)	MDR1 ↓[m] ↓[p]	(Xu et al., 2012)
		Colorectal adenocarcinoma SW480 cells	MDR1 ↓[m] ↓[p] BCRP ↔[m] ↔[p]	(Ye et al., 2016)
		Colorectal carcinoma HCT-116 cells	MDR1 ↓/↑[m] ↓/↑[p] BCRP ↔[m] ↔[p]	(Xu et al., 2012; Ye et al., 2016)
		Colorectal carcinoma HCT-116 cells (R)	MDR1 ↔[m] ↔[p]	(Xu et al., 2012)
		Cervical adenocarcinoma HeLa cells	MDR1 ↑[m] ↑[p]	(Kim et al., 2009)
		Glioblastoma/Astrocytoma U87 cells	MDR1 ↔[m] ↔[p] BCRP ↔[m] ↔[p]	(Zhang et al., 2016)
		Glioblastoma A172 cells	MDR1 ↔[m] ↔[p] BCRP ↔[m] ↔[p]	(Zhang et al., 2016)
		Placental choriocarcinoma BeWo cells	MDR1 ↑[m] ↑[p] ↑[a]	(Duan et al., 2017b)
		Placental choriocarcinoma JAR cells	MDR1 ↑[m] ↑[p] ↑[a]	(Duan et al., 2017b)
HDAC3	siRNA	Melanoma Malme3M cells	MDR1 ↑[p]	(Park et al., 2014)
		Hepatocellular carcinoma SNU387 cells	MDR1 ↑[p]	(Park et al., 2014)
		Placental choriocarcinoma BeWo cells	MDR1 ↔[m] ↔[p] ↔[a]	(Duan et al., 2017b)
		Placental choriocarcinoma JAR cells	MDR1 ↔[m] ↔[p] ↔[a]	(Duan et al., 2017b)
HDAC6	siRNA	Melanoma Malme3M cells (R)	MDR1 ↓[p]	(Kim et al., 2015)
		Hepatocellular carcinoma SNU384 cells (R)	MDR1 ↓[p]	(Kim et al., 2015)
HDAC8	siRNA	Glioblastoma/Astrocytoma U87 cells	MDR1 ↓[m]	(Zhao et al., 2017)
		Neuroblastoma SH-SY5Y cells	MDR1 ↓[m]	(Zhao et al., 2017)
		Neuroblastoma SK-N-SH cells	MDR1 ↓[m]	(Zhao et al., 2017)

m: mRNA; p: Protein; a: Activity


Sp1, Sp3
-200
-100
+1
+200
+300
5'
3'
C/EBP
CAAT
p53
GC
p53
NF-κB
AP-1
GC
Y box
DRE*
TSS
DRE*
Sp1, Sp3
NF-Y
AHR
AHR


PR
ER
-400
AP-1
-300
CAAT
Sp1
-200
PRE
ERE
Sp1
-100
Sp1
+1
5'
3'
CpG island
DRE
Sp1
HRE
AP-2
NF-κB
TSS
AHR